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(54) 4,5,6,7-Tetrahydro-1H-imidazo[4,5-c]pyridine derivatives and analogs having antihypertensive activity.

(57) This invention relates to novel substituted derivatives of 4,5,6,7-tetrahydro-1*H*-imidazo [4,5-c]-pyridine and analogs thereof, which are useful for the treatment of hypertension, as well as, novel pharmaceutical compositions and methods of use.

NEW IMIDAZO-(4,5-C)-TETRAHYDRO-PYRIDINE(S) AND ANALOGUES + USEFUL AS ANTIHYPERTENSIVES

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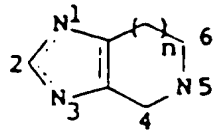
DESCRIPTION TITLE MODIFIED see front page

This invention relates to novel substituted derivatives of 4,5,6,7-tetrahydro-1H-imidazo[4,5-c]-pyridine-6-carboxylic acid and analogs thereof which are useful for the treatment of hypertension. US Patent 4,141,899 to Arcari et al. issued February 27, 1979, discloses 4,5,6,7-tetrahydroimidazo[4,5-c]-pyridine derivatives as antiulcer and antisecretory agents. Further examples are disclosed in Arzneim. Forsch. 34 (11) 1467-1471 (1984). These compounds differ from the ones disclosed in this invention in that they lack a substituent group at the 6-position. This variation, in combination with substitution at other positions of the imidazo[4,5-c]pyridine ring provide novel compounds now found to have anti-hypertensive activity. Japanese Patent applications J5 9095-286A to Otsuka Seiyaku Kojy, published January 6, 1984, discloses imidazo[4,5-c]pyridine 6-carboxylic acid derivatives having psycholeptic, hypotensive, central nervous system or analeptic activity.

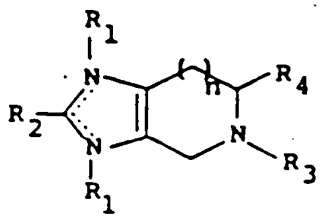
A Belgian Patent No. 902,611 entitled "New Imidazo-Pyridine-6-Carboxamide Derivatives Useful as Antiviral Agents" discloses related compounds limited to an amide function in a C_6 position of a nuclear structure having the positions numbered as shown in the formula as follows:



Such compounds limited to the amide function are disclosed by Belgian Patent No. 902,611 as pharmaceutically active agents. Additionally related compounds having a carboxyl function at the C_6 position are disclosed by the Belgian Patent No. 902,611 but only for use as intermediates.

Thus the compounds of the first three of the above references differ from those disclosed in this invention by virtue of bearing no substituent groups at N_1, N_3, N_5, or C_4; but carrying a spiro ring at C_4. Further the present invention excludes compounds having a carboxylic acid group disclosed only as intermediates in Belgian Patent No. 902,611 discussed above. The present invention is thus pharmaceutical compositions having compounds of formula I' as defined hereinafter and a pharmaceutically acceptable carrier and method of use therefor. Such differences provide unobvious variance over the prior art.

The present invention is a novel analog of 4,5,6,7-tetrahydroimidazo[4,5-c]pyridine having the formula (I):



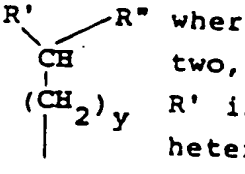
I

and their pharmaceutically acceptable base or acid addition salts; wherein

(1) - - - is a single or double bond;

(2) one of R_1 is present and is

(a) alkyl of from four to twenty carbons, inclusive,

(b)  wherein y is zero, one, two, three, four or five, R' is cycloalkyl, naphthyl, heteroaryl, phenyl unsubstituted or substituted with of from one through five, preferably one through three, substituents comprising lower alkyl, halo, trifluoromethyl, hydroxy, lower alkoxy, lower acyloxy, amino, N-lower monoalkylamino, N,N-lower dialkylamino, lower thioalkyl, lower alkylsulfonyl, nitro or $-NHCR_{10}$ wherein R_{10} is lower alkyl, phenyl unsubstituted or substituted by lower alkyl, or $-NHR_{11}$ wherein R_{11} is hydrogen or lower alkyl, and R" is hydrogen, lower alkyl, cycloalkyl, naphthyl, phenyl unsubstituted or substituted with of from one through five substituents, preferably from one through three substituents, comprising alkyl, halo, trifluoromethyl, amino, N-lower monoalkylamino, N,N-lower dialkylamino, lower thioalkyl, lower alkylsulfonyl, or nitro;

(3) R_2 is

(a) hydrogen,

(b) halo,

(c) lower alkyl,

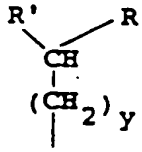
(d) $R'-(CH_2)_x$ wherein x is one, two, three, four, or five and R' is independently as defined above,

(e) $R'-\overset{O}{\overset{\|}{C}}-$ wherein R' is independently as defined above, or

(f) R'-CH(OH)- wherein R' is independently as defined above;

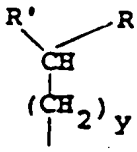
(4) R_3 is

(a) $R'-(CH_2)_x$ wherein x and R' are independently as defined above,

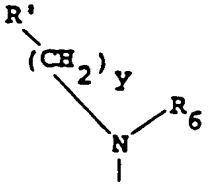
(b)  wherein R' and y are independently as defined above, and R'" is lower alkyl, cycloalkyl, naphthyl, phenyl unsubstituted or substituted with of from one through five substituents, preferably from one through three substituents, comprising alkyl, halo, trifluoromethyl, amino, N-lower monoalkylamino, N,N-lower dialkylamino, lower thioalkyl, lower alkylsulfonyl, or nitro;

(c) $-\overset{O}{\overset{\|}{C}}-R_5$ wherein R_5 is

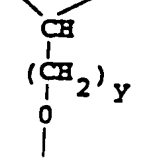
(i) alkyl of from one to fifteen carbons, inclusive,

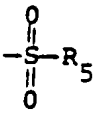
(ii)  wherein R', R" and y are independently as defined above,

(iv) $-(CH=CR_6)-R_1$, wherein R_6 is hydrogen or lower alkyl and R_1 is as defined above,

(v)  wherein y, R' and R_6 are independently as defined above,

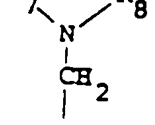
(vi) $R'-(CH_2)_y-O-$ wherein y and R' are independently as defined above,

(vii)  wherein R', R", and y are independently as defined above,

(d)  wherein R_5 is independently as defined above, preferably $R'-(CH_2)_y$ wherein R' and y are independently as defined above;

(5) R_4 is

(a) $-CH_2OR_7$ wherein R_7 is hydrogen, lower acyl, a lower alkyl,

(b)  wherein R_7 is independently as defined above and R_8 is hydrogen, lower alkyl, or benzyl,

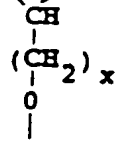
(c) $-\overset{O}{\overset{\|}{C}}H$,

(d) $-C\equiv N$,

(e) $-\overset{O}{\overset{\|}{C}}OR_9$ wherein R_9 is hydrogen, lower alkyl or benzyl; and

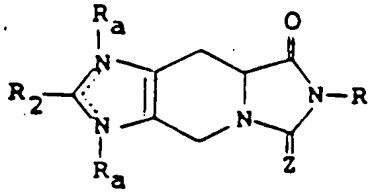
(6) n is zero, one, two, or three; with the overall proviso that R_9 cannot be hydrogen

when R_3 is $R'-(CH_2)_x-$ or $-\overset{O}{\overset{\|}{C}}-R_5$ wherein R_5 is $R'-(CH_2)_y-O-$ or



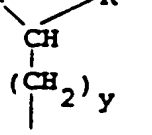
each of R', R", x and y are as defined above.

Further, the present invention is a novel compound of formula (II):



II

and the nontoxic, pharmaceutically acceptable base or acid addition salts thereof, wherein ---- is as defined above;

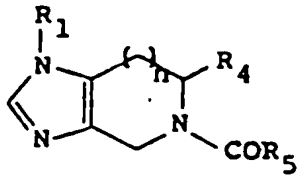
(1) one of R_a is present and is
  (a) hydrogen,
  (b) alkyl of from one to twenty carbons, inclusive,
  (c)  wherein y, R' and R" are independently as defined above; and

(2) Z is oxygen or sulfur; and

(3) R_2 is independently as defined above.

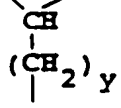
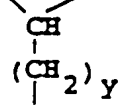
(4) R is lower alkyl, heteroaryl, phenyl or benzyl each unsubstituted or substituted with of from one through five, preferably one through three, substituents comprising lower alkyl, halo, trifluoromethyl, hydroxy, lower alkoxy, lower acyloxy, amino, N-lower monoamino, N,N-lower dialkylamino, lower thioalkyl, lower alkylsulfonyl, or nitro.

The compounds of formula I, that are preferred, are those wherein R_2 is H, R_3 is  and n is one or two, or more particularly, the preferred compounds of formula I, that are preferred, have the formula (XX)



XX

wherein R_1, n, R_4 and R_5 are as defined above.

More preferred are the compounds of formula XX wherein R_1 is  wherein R' is phenyl unsubstituted or substituted as defined above, R" is hydrogen and y is zero, one, or two, and R_5 is  wherein R', R" and y are as defined above.

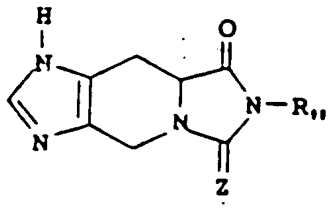
The novel compounds of formula II of the present invention are intermediates useful in the preparation of selected derivatives shown above as novel compounds having the formula I as defined above.

Additionally, the present invention has found that selected intermediates that are novel compounds of formula II as defined above also possess useful antihypertensive activity.

Thus, the preferred compounds of formula II according to the present invention are compounds

that are (1) intermediates useful in the preparation of preferred compounds of formula I and (2) compounds having use as antihypertensive agents.

The compounds of formula II having antihypertensive activity are those having the formula (IIa)

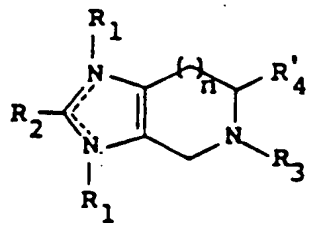


IIa

wherein Z is as defined above and R_{11} is branched alkyl of from three to five carbons, inclusive, and unsubstituted and substituted phenyl as defined above, preferably phenyl substituted by one to three methoxy substituents, inclusive.

The present invention is also directed to novel processes for the preparation of the compounds of the present invention. That is, the processes for the preparation of compounds of the formula I and the processes for the preparation of compounds of the formula II are both the present invention.

Additionally, the present invention is directed to a pharmaceutical composition for treating hypertension in mammals comprising an antihypertensive effective amount of the compound of formula (I')



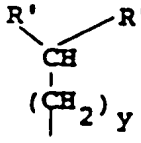
I'

and their pharmaceutically acceptable base or acid addition salts; wherein

(1) - - - is a single or double bond;

(2) one of R_1 is present and is

(a) alkyl of from four to twenty carbons, inclusive,

(b)  wherein y is zero, one, two, three, four or five, R' is cycloalkyl, naphthyl, heteroaryl, phenyl unsubstituted or substituted with of from one through five, preferably one through three, substituents comprising lower alkyl, halo, trifluoromethyl, hydroxy, lower alkoxy, lower acyloxy, amino, N-lower monoalkylamino, N,N-lower dialkylamino, lower thioalkyl, lower alkylsulfonyl, nitro or $-NHC(=O)R_{10}$ wherein R_{10} is lower alkyl, phenyl unsubstituted or substituted by lower

alkyl, or $-NHR_{11}$ wherein R_{11} is hydrogen or lower alkyl, and R" is hydrogen, lower alkyl, cycloalkyl, naphthyl, phenyl unsubstituted or substituted with of from one through five substituents, preferably from one through three substituents, comprising alkyl, halo, trifluoromethyl, amino, N-lower monoalkylamino, N,N-lower dialkylamino, lower thioalkyl, lower alkylsulfonyl, or nitro;

(3) R_2 is

(a) hydrogen,

(b) halo,

(c) lower alkyl,

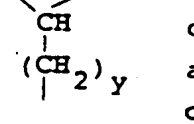
(d) $R'-(CH_2)_x$ wherein x is one, two, three, four, or five and R' is independently as defined above,

(e) $R'-\overset{O}{\overset{\|}{C}}-$ wherein R' is independently as defined above, or

(f) R'-CH(OH)- wherein R' is independently as defined above;

(4) R_3 is

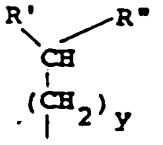
(a) $R'-(CH_2)_x$ wherein x and R' are independently as defined above,

(b)  wherein R' and y are independently as defined above, and R'" is lower alkyl, cycloalkyl, naphthyl, phenyl unsubstituted or substituted with of from one through five substituents,

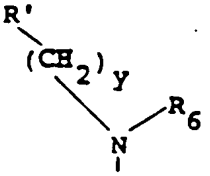
preferably from one through three substituents, comprising alkyl, halo, trifluoromethyl, amino, N-lower monoalkylamino, N,N-lower dialkylamino, lower thioalkyl, lower alkylsulfonyl, or nitro;

(c) $-\overset{O}{\overset{\|}{C}}-R_5$ wherein R_5 is

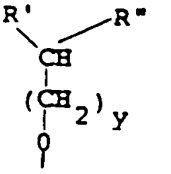
(i) alkyl of from one to fifteen carbons, inclusive,

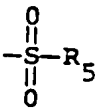
(ii)  wherein R', R" and y are independently as defined above,

(iv) $-(-CH=CR_6-)- R_1$, wherein R_6 is hydrogen or lower alkyl and R_1 is as defined above,

(v)  wherein y, R' and R_6 are independently as defined above,

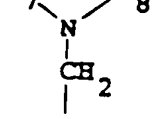
(vi) $R'-(-CH_2-)_y-O-$ wherein y and R' are independently as defined above,

(vii)  wherein R', R", and y are independently as defined above,

(d)  wherein R_5 is independently as defined above, preferably $R'-(-CH_2-)_y$ wherein R' and y are independently as defined above;

(5) R_4' is

(a) $-CH_2OR_7$ wherein R_7 is hydrogen, lower acyl, a lower alkyl,

(b)  wherein R_7 is independently as defined above and R_8 is hydrogen, lower alkyl, or benzyl,

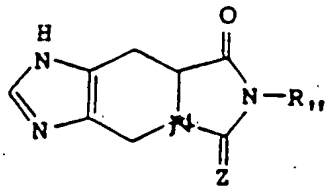
(c)  ,

(d) $-C\equiv N$,

(e)  wherein R_9' is hydrogen, lower alkyl or benzyl; and

(6) n is independently as defined above, together with a pharmaceutically acceptable carrier.

The present invention is also directed to a pharmaceutical composition for treating hypertension in mammals comprising an antihypertensive effective amount of selected compounds of formula II which selected compounds have formula (IIa)



IIa

and the nontoxic, pharmaceutically acceptable base or acid addition salts thereof, wherein Z is oxygen or sulfur and R_{11} is branched alkyl of from three to five carbons, inclusive, and phenyl substituted with of from one through five, preferably one through three, substituents comprising lower alkyl, halo, trifluoromethyl, hydroxy, lower alkoxy, lower acyloxy, amino, N-lower monoamino, N,N-lower dialkylamino, lower thioalkyl, lower alkylsulfonyl, or nitro; together with a pharmaceutically acceptable carrier.

Also the present invention is directed to the use of a compound of formula I' for the manufacture of a medicament for treating hypertension in mammals suffering therefrom.

In the compounds of the formula I or of the formula II, the term alkyl of from one to twenty and one to fifteen carbons is meant to include a straight or branched alkyl group having the noted number of carbons, such as, for example, methyl, ethyl, propyl, butyl, pentyl, hexyl and the like and isomers thereof.

Halo includes particularly fluorine, chlorine or bromine.

Lower alkyl is methyl, ethyl, propyl, or butyl and isomers thereof.

Lower alkoxy is -O-alkyl wherein alkyl is lower alkyl.

Lower thioalkyl is -S-alkyl wherein alkyl is lower alkyl.

Lower acyloxy is alkyl —C(=O)—O- wherein alkyl is lower alkyl.

Lower alkylsulfonyl is alkyl —S(=O)(=O)- wherein alkyl is lower alkyl.

Heteroaryl is 2-, 3-, or 4-pyridyl; 1-, 2-, or 4-imidazolyl; 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl; 2-, or 3-thienyl; 2-, or 3-furyl; or 1-, 2-, or 3-pyrazolyl and the like.

Cycloalkyl is of from four to twenty carbons, inclusive in a one, two or three saturated ring system, said ring comprising from four to eight carbons, inclusive, including monocyclo rings such as cyclobutyl, cyclopentyl, cyclohexyl and the like,

or polycyclo rings such as adamantyl or norbornyl. Each ring may be unsubstituted or substituted by a straight or branched lower alkyl group.

The compounds of formula I are useful both in the free base form, in the form of base salts where possible, and in the form of acid addition salts. The three forms are within the scope of the invention. In practice, use of the salt form amounts to use of the base form. Appropriate pharmaceutically acceptable salts within the scope of the invention are those derived from mineral acids such as hydrochloric acid and sulfuric acid; and organic acids such as methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, and the like, giving the hydrochloride, sulfate, methanesulfonate, benzenesulfonate, p-toluenesulfonate, and the like, respectively or those derived from bases such as suitable organic and inorganic bases. Examples of suitable inorganic bases for the formation of salts of compounds of this invention include the hydroxides, carbonates, and bicarbonates of ammonia, sodium, lithium, potassium, calcium, magnesium, aluminum, zinc, and the like.

Salts may also be formed with suitable organic bases. Bases suitable for the formation of pharmaceutically acceptable base addition salts with compounds of the present invention include organic bases which are nontoxic and strong enough to form such salts. These organic bases form a class whose limits are readily understood by those skilled in the art. Merely for purposes of illustration, the class may be said to include mono-, di-, and trialkylamines,

such as methylamine, dimethylamine, and triethylamine; mono-, di- or trihydroxyalkylamines such as mono-, di- and triethanolamine; amino acids such as arginine, and lysine; guanidine; N-methylglucosamine; N-methylglucamine; L-glutamine; N-methylpiperazine; morpholine; ethylenediamine; N-benzylphenethylamine; tris(hydroxymethyl)aminomethane; and the like. (See for example, "Pharmaceutical Salts," J. Pharm. Sci. 66 (1):1-19 (1977).)

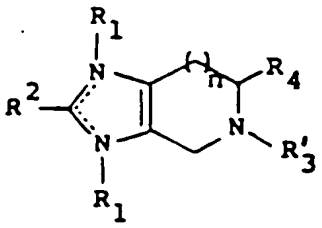
The acid addition salts of said basic compounds are prepared either by dissolving the free base of compound I, I' or II in aqueous or aqueous alcohol solution or other suitable solvents containing the appropriate acid or base and isolating the salt by evaporating the solution, or by reacting the free base of compound I, I', or II with an acid as well as reacting compound I, I' or II having an acid group thereon with a base such that the reactions are in an organic solvent, in which case the salt separates directly or can be obtained by concentration of the solution.

The compounds of the invention may contain an asymmetric carbon atom. Thus, the invention includes the individual stereoisomers, and the mixtures thereof. The individual isomers may be prepared or isolated by methods known in the art.

The novel processes of the present invention are described, generally, as follows:

Method A:

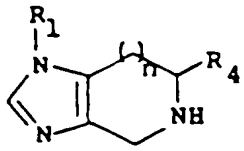
In a process for the preparation of a compound having the formula



I'

wherein R_1, n and R_4 are as defined above and R'_3 is $-\overset{O}{\overset{\|}{C}}R_5$ or $-\overset{O}{\overset{\|}{\underset{O}{\overset{\|}{S}}}}R_5$ wherein R_5 is as defined above;

a compound of formula III shown below wherein R_1, n, and R_4 are as defined above, is acylated using an appropriately activated acylating derivative of R_5CO_2H or R_5SO_3H.



III

Preferred methods use dicyclohexylcarbodiimide to activate the R_5CO_2H for reaction with a compound of formula III using modifications known in the art; or involve preparation of acylhalides such as $R_5\overset{O}{\overset{\|}{C}}$-Hal wherein Hal is halo, preferably chloro or bromo; or involves preparation of $R_5\overset{O}{\overset{\|}{\underset{O}{\underset{\|}{S}}}}$-Hal, wherein Hal is halo, preferably chloro or bromo, or involves preparation of mixed or symmetrical anhydrides, for reaction with a compound of formula III. The reaction is carried out in nonaqueous solvent, such as acetonitrile, tetrahydrofuran or methylene chloride, with an added organic base, such as triethylamine or pyridine, if needed at temperatures between -10°C and the reflux temperature of the solvent. Alternatively, the compound of formula III wherein R_4 is CO_2H may be acylated in aqueous basic solution with selected compounds of the formula $R\overset{O}{\overset{\|}{C}}$-Hal or $R\overset{O}{\overset{\|}{\underset{O}{\underset{\|}{S}}}}$-Hal.

For compounds of formula I' wherein R_4 defined as CO_2H is desired, compounds wherein R_4 is $COOR_9$ wherein R_9 is lower alkyl or benzyl may be hydrolyzed under mildly acidic or basic conditions using standard procedures known in the literature.

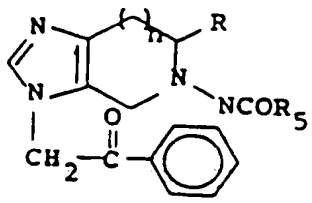
Compounds of formula III are obtained by reacting π-R_1-substituted histidine derivatives with formaldehyde or a formaldehyde equivalent such as dimethoxymethane in the presence of a strong acid such as hydrochloric acid. The reaction is carried out in aqueous medium at temperatures between 0°C and the refluxing temperature

of the solvent. Compounds III wherein R_4 is COOH are isolated and may be esterified using lower alkanols. The acid of formula III having R_4 as $COOR_9$ wherein R_9 is lower alkyl or benzyl may be reduced to form a compound wherein R_4 is CH_2OH using standard methods known in the art. π-R_1-substituted histidines are known or may be prepared by a variety of methods known in the literature, (Rec. Trav. Chim., 1972, 91, p. 246). When n is 2 then the homo histidine (Peptides Symp: Proc. 11th Eur. Peptide Symposium (1973) p. 351) is used as a starting material.

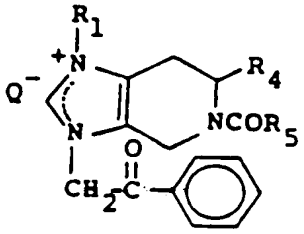
Method B:

An alternative procedure for obtaining compounds of the invention having the formula I or II wherein R_1, R_4, R_5 and n defined in a manner corresponding to IV and V below consists of treating a compound of formula IV as shown below wherein R_4, R_5, and n are as defined above, with R_1-Q, wherein Q is a leaving group suitable to be an alkylating agent, such as discussed below, and then treating the intermediate salt, a compound of the formula V, wherein R_1, R_4, R_5 and n are as defined above, with a reducing agent, preferably zinc in an acidic medium.

The compounds of formula IV or V are as follows:



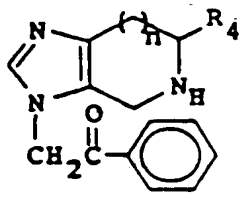
IV



V

Suitable alkylating agents are R_1-Q wherein R_1 is as defined above and Q may be halo, or sulfonate and trifluorosulfonate esters of R_1-OH wherein R_1 is as defined above. The substituent R_4 of the compound of formula I may then be processed by hydrolysis as needed. This method may also be used to prepare intermediates of formula III as shown and defined above for use in Method A. In this case, the group $R_5\overset{O}{\overset{\|}{C}}-$ is removed by hydrolysis, typically under aqueous acidic conditions within the skill of the ordinary artisan. Intermediates of the formula IV as shown and defined above are prepared by a similar sequence of reactions described for the preparation of the compounds of formula III above; namely acylation of a compound of formula VI as shown below wherein R_4 is as defined above, which is formed by an acidic formaldehyde ring formation reaction with τ-phenacyl histidine, a compound

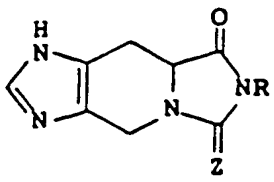
described in the literature, (J. Chem. Soc., Per I (1979) p. 2261).



VI

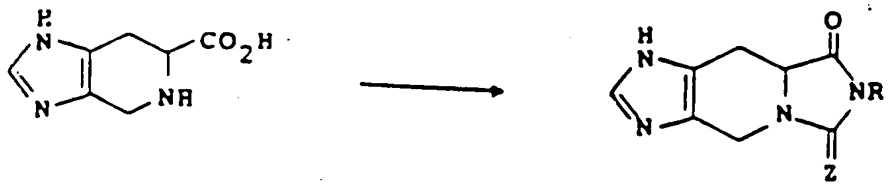
Method C:

Still another alternate procedure by which the compounds having formula I or formula II of this invention may be obtained, as well as intermediates III and IV cited above, consists of treating 4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylic acid also known as spinacine or the lower alkyl ester thereof described in (Hoppe-Seyler Zeitschrift. Physiol. Chem. (1949) vol. 284, p. 129) with an isocyanate or isothiocyanate of the formula RN=C=O or RN=C=S respectively, to give a compound of the formula (VII)



VII

wherein Z and R are as defined above. Selected compounds of formula II as described in the second part of this invention are prepared in this manner and may be shown as follows:

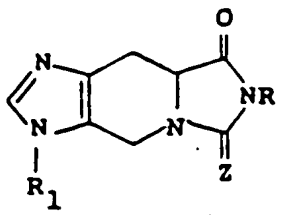


Spinacine

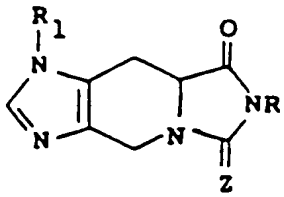
VII

Compounds of formula VII as defined above are then further converted to compounds of formula I, by treatment with an alkylating agent R_1-Q, as described in Method B, in the presence of a strong base, typically

sodium or potassium hydride or sodium alkoxide in polar aprotic solvent, such as tetrahydrofuran, dimethylformamide or the like to give a mixture of a compound of formula VIII wherein Z, R, and R_1 are as defined above and a compound of formula IX wherein Z, R_1, and R are as defined above which can be separated by crystallization or chromatography.

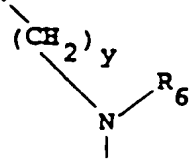


VIII



IX

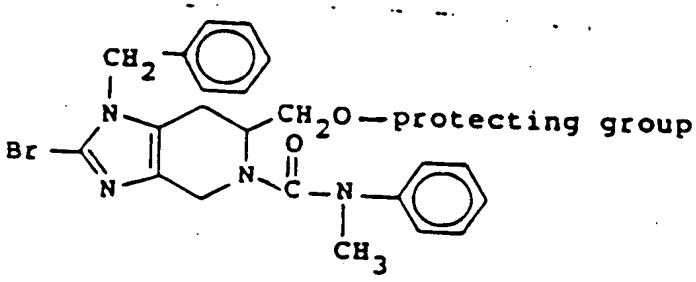
The compounds of formula VIII or IX are then in turn hydrolyzed under moderate basic conditions, e.g., alkali hydroxide in aqueous alcoholic medium at reflux until solution occurs, to give compounds of formula I wherein R_5 is R' wherein R'



and y are as defined above and R_6 is H; or under more vigorous basic conditions, e.g., concentrated alkali hydroxide treated for prolonged periods under

reflux, to give intermediates of formula III wherein R_4 is CO_2H. It should be appreciated that intermediates of formula III and VI both as shown and defined above may also be directly converted to compounds of formula VIII or IX also as shown and defined above by reaction with isocyanates or isothiocyanates.

Compounds of the formula I or II of the invention wherein R_2 is other than H may be prepared by transformations of intermediates already described. Thus, compounds of the formula I wherein R_2 is H, R_1 is as defined above, R_4 is CH_2OR_7 and R_3 is COR_5; VIII or IX both as shown and defined above, can be treated with a brominating agent such as bromine or N-bromosuccinimide in a solvent to give a compound of formula I wherein R_2 is Br or a compound of the formula II wherein R_2 is Br. Especially useful is the intermediate of the formula X as shown and defined below,



X

(the preferred protecting group is trialkylsilyl)

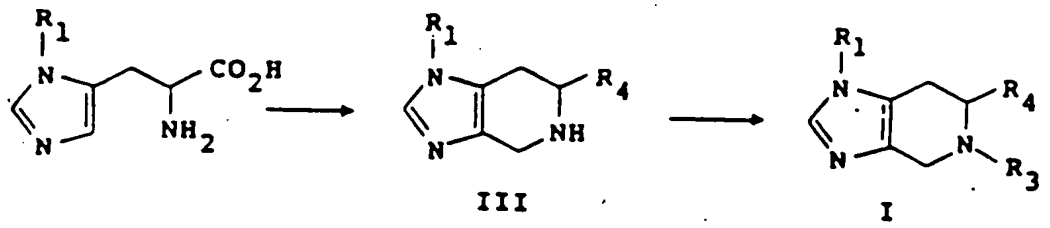
which may be further treated with an alkyllithium reagent, preferably n-butyllithium in an anhydrous

solvent at low temperature to form a lithio derivative which may react with an alkylating agent R_2-Q, where Q is as described above, an aldehyde or ketone, or an appropriate carboxylic acid derivative to install other R_2 moieties as described above. Further processing of the intermediate of formula X to compounds I defined above follows the procedures disclosed under Methods A, B, or C above.

Alternatively, compounds of formula VIII or IX both as defined above wherein Z is O, may be reacted with an aroylhalide in an aprotic solvent in the presence of a tertiary organic base such as triethylamine to give compounds of formula II where R_2 is $R'-\overset{O}{\overset{\|}{C}}-$ wherein R' is as defined above. This group may be further reduced and deoxygenated using methods known in the art to provide other R_2 substituents as defined above.

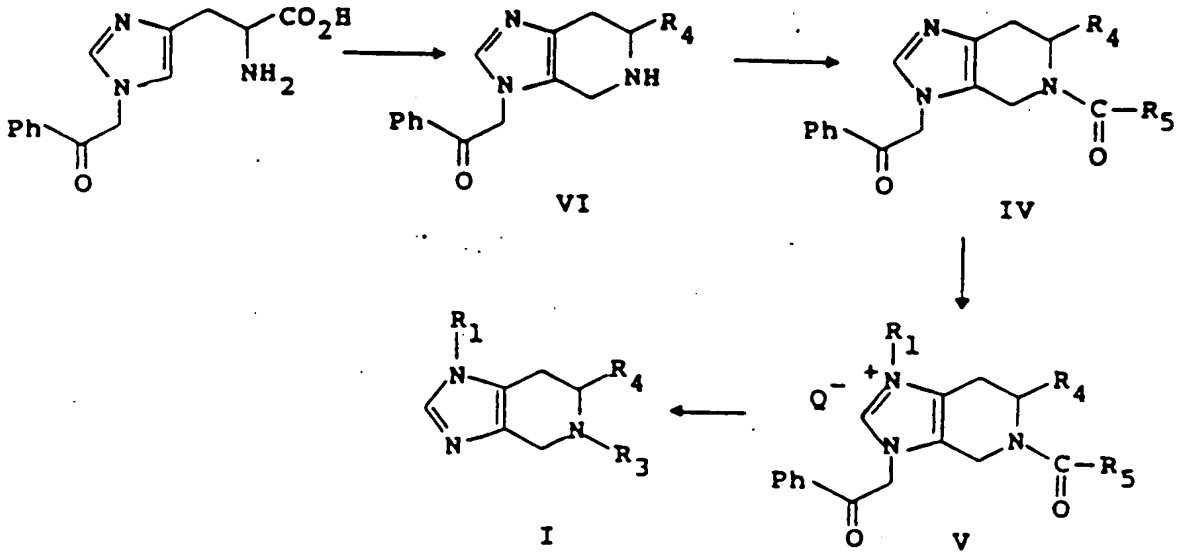
A summary of the above described general methods of preparation can be shown by the following schematic.

Method A



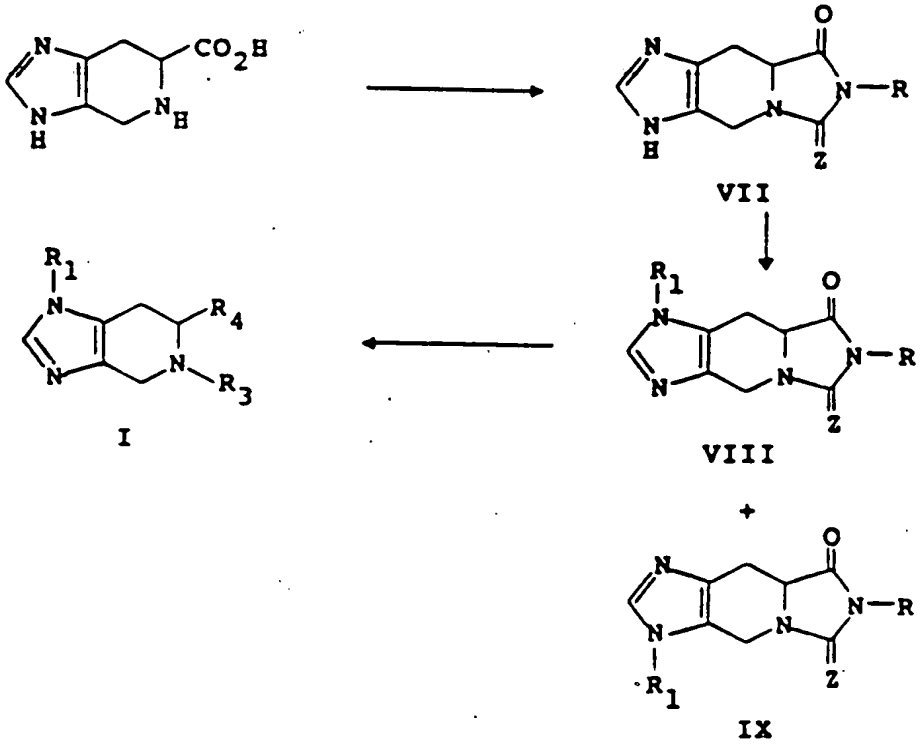
III I

Method B



VI IV V I

Method C



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Under certain circumstances it is necessary to protect either the N or O of intermediates II and III in the above noted process with suitable protecting groups which are known. Introduction and removal of such suitable oxygen and nitrogen protecting groups are well-known in the art of organic chemistry; see for example, (1) "Protective Groups in Organic Chemistry," J. F. W. McOmie, ed., (New York, 1973), pp. 43ff, 95ff; (2) J. F. W. McOmie, Advances in Organic Chemistry, 3:191-281 (1963); (3) R. A. Borssonas, Advances in Organic Chemistry, 3:159-190 (1963); and (4) J. F. W. McOmie, Chem. & Ind., 603 (1979).

Examples of suitable oxygen protecting groups are benzyl, t-butyldimethylsilyl, methyl, isopropyl, ethyl, tertiary butyl, ethoxyethyl, and the like. Protection of an N-H containing moiety is necessary for some of the processes described herein for the preparation of compounds of this invention. Suitable nitrogen protecting groups are benzyl, triphenylmethyl, trialkylsilyl, trichloroethylcarbamate, trichloroethoxycarbonyl, vinyloxycarbamate, and the like.

In the process described herein for the preparation of compounds of this invention the requirements for protective groups are generally well recognized by one skilled in the art of organic chemistry, and accordingly the use of appropriate protecting groups is necessarily implied by the processes of the charts herein, although not expressly illustrated.

The products of the reactions described herein are isolated by conventional means such as extraction, distillation, chromatography, and the like. Generally,

the starting materials are known, can be purchased commercially, or synthesized by known methods.

The compounds of formula I and of formula IIa and the pharmaceutically acceptable base or acid addition salts thereof are useful as antihypertensive agents for the treatment of high blood pressure.

PHARMACOLOGICAL EVALUATION

The usefulness of the compounds of the present invention having formula I and IIa as antihypertensive agents is demonstrated by their effectiveness in standard pharmacological test procedures, for example, in inhibiting of ^{125}I-angiotensin II binding or in causing a significant decrease in mean arterial blood pressure in the conscious rat either in a 2 kidney, 1-clip Goldblatt hypertensive rat (RHR) or a spontaneously hypertensive rat (SHR).

Thus, for example, compounds of formula I when administered intraperitoneally or orally to 2 kidney, 1-clip Goldblatt (renal) hypertensive rats (See S. Sen, et al., "Role of Renin-Angiotensin System in Chronic Renal Hypertensive Rats," Hypertension 1:427-434 (1979) and Clin. Soc. 57:53-62, 1979, "Antihypertensive Effect of Prolonged Blockade of Angiotensin Formation in Benign and Malignant, one- and two-kidney Goldblatt Hypertensive Rats".) at doses in the range of 1-100 mg/kg cause 10-80 mmHg drops in blood pressure. Compounds of formula I have also been shown to antagonize the binding of angiotensin II to rat adrenal receptor preparations (procedure of J.G. Douglas et al., Endocrinology,

106, 120-124 (1980)). Compounds which antagonize the action of angiotensin II, an endogenous pressor peptide, are known to be effective antihypertensive agents (I. Reid., Arch. Int. Med., 145, 1475-1479 (1985); N. K. Hollenberg, Am. Rev. Pharmacol. Toxicol., 19, 559-582 (1979)). In addition, compounds of formula II, although not possessing this later property, have been shown to lower blood pressure in spontaneously hypertensive rats at doses of 1-100 mg/kg orally. This test has been shown to be a good predictor of antihypertensive activity in man (See K.O. Kamoto, ed., "Spontaneous Hypertension--Its Pathogenesis and Complications", Igaku Shoin Ltd., Tokyo, Springer Verlag, Berlin, Heidelbert, N.Y. and H.J. Baker et al, ed., The Laboratory Rat Vol II. "Research Applications", American College of Laboratory Animal Medicine Series, Academic Press, 1980, pp. 168-170.). Angiotensin binding inhibition activity and blood pressure lowering activity in renal hypertensive rats of the optimally substituted examples of formula I are listed in Table 1. Blood pressure lowering activity in spontaneously hypertensive rats of optimally substituted examples of formula II are listed in Table 2.

Specifically, the protocol for the test procedures resulting in the data of Tables 1 and 2 is as follows:

ANTIHYPERTENSIVE EVALUATION (AHP3)

A Method for the Direct Monitoring of Aortic Blood Pressure and Heart Rate from Conscious Rats

The continuous monitoring of pulsatile blood pressure (BP) from unrestrained conscious rats surgically equipped with polyethylene cannulas was accomplished by means of a computer assisted data capture scheme (CADCS). The basic elements of the methodology are the cannulation procedure and the CADCS.

Method

Cannulation Procedure: Rats were anesthetized with Telazol (1:1 tiletamine HCl and zolazepam HCl); 20-40 mg/kg IM and the descending aorta exposed via a midline incision. Cannulas fabricated from polyethylene tubing were inserted into the aorta via an undersized puncture hole below the renal arteries. The puncture hole was made by a 23 G disposable needle with a section of the aorta clamped off above and below the puncture site. The cannulas, consisting of a PE100 (0.86 mm ID) body and a PE50 (0.58 mm ID) tip, were attached to a trocar, inserted through the psoas muscle, and passed subcutaneously along the midline of the back and externalized between the ears. The cannulas were anchored to the psoas muscle and between the scalulae (3-0 green braided suture). The midline incision was closed in two steps (muscle first, skin second) using continuous over-and-over sutures (4-0 chronic). Each rat was then given penicillin 30,000 units subcutaneously (Penicillin G Procaine Sterile Suspension).

The rats were fitted with a harness-spring-swivel assembly designed to protect the cannula

and to provide the rat relative freedom of movement. The harnesses were fabricated from nylon hook and loop tape cemented to a metal plate to which spring wires (18-8 stainless steel), were attached to brass swivels. Each polyethylene cannula was channeled through a spring and connected through a swivel to a pressure transducer (Model P23Gb; Statham Instruments; Hato Rey, Puerto Rico) and an infusion pump (Sage model 234-7; Orion Research, Cambridge, MA) by means of PE100 tubing. While on test, each rat received a continuous slow infusion of heparinized saline solution (approximately 0.40 ml or 40 units of heparin per 24 hr period) to prevent clot formation. Additional "flushes" of the cannula with heparinized saline were carried out when the aortic pulse pressure (systolic minus diastolic) was less than 25 mm Hg.

CADCS: The pulsatile blood pressure of each of 32 rats was monitored continuously by two signal conditioning units (Gould, Clev., Ohio). The signals from these units were monitored and digital data for mean, systolic, and diastolic blood pressures as well as for heart rate were calculated every 5 min by two in-laboratory computers (Hewlett Packard, Cupertino, Ca.). These in-laboratory computers have the capacity to store 32 days of this 5 min data. Communication with the mainframe research computer (IBM 3083) from the two in-laboratory computers allowed for data analysis and report generation. The overall scheme involved modulating the primary signal from the pressure transducer, calculating the 5 min data values for

mean, systolic, and diastolic blood pressures as well as heart rate by the in-laboratory computers and generating summary data on the mainframe research computer.

In order to monitor the effects of drugs on blood pressure or heart rate, either spontaneously hypertensive rats (SHR) or renin-dependent 2 kidney, 1-clip Goldblatt hypertensive rats (RHR) were dosed intraperitoneally or orally with test compounds. Rats were dosed once daily for up to 3 consecutive days and hemodynamic variables were continuously monitored for up to 24 hr following the last day of dosing.

TABLE I
ANTI HYPERTENSIVE ACTIVITY OF COMPOUNDS OF FORMULA I

EXAMPLE Number	R_1	R_3	R_4	IC_{50} (μM)*	Max % decrease in blood pressure 30 mg/kg ip in RHR**
169	CH_2Ph	$COCHPh_2$	CO_2H	1.0	-20
22	CH_2Ph	$COCH(Ph\text{-}4Cl)_2$	CO_2H	6.8	-27
29	CH_2Ph	CO(9-fluorenyl)	CO_2H	8.0	-22
13	CH_2((4-NH_2, 3-Me)Ph)	$COCHPh_2$	CO_2H	0.06	-22
278	CH_2Ph	CON(Me)Ph	CH_2OH	1.6	-22
2	CH_2CH_2-(1-adamantyl)	$COCHPh_2$	CO_2H	0.10	-26
21	CH_2(4-CF_3Ph)	$COCHPh_2$	CO_2H	0.19	-18
4	CH_2CH_2-cyclohexyl	$COCHPh_2$	CO_2H	0.24	-13
75	CH_2(3-CH_3Ph)	$COCHPh_2$	CO_2H	0.27	-30
279	CH_2((4-OCH_3, 3-Me)Ph)	$COCHPh_2$	CH_2OH	0.37	-25
17	CH_2(2-OHPh)	$COCHPh_2$	CO_2H	0.69	-21
24	CH_2((4-OMe, 3Me)Ph)	COCH(Ph)cyclohexyl	CO_2H	0.07	-16
26	CH_2((4-OMe, 3Me)Ph)	$COCH_2$cyclohexyl	CO_2H	2.0	-18
23	CH_2Ph	$COCH(Ph\text{-}4F)_2$	CO_2H	2.1	-22
19	CH_2((4-OMe, 3Me)Ph)	$COCHPh_2$	CO_2H	0.07	-14
6	CH_2CH_2Ph	$COCH_2Ph$	CO_2H	2.4	-16
25	CH_2((4-OMe, 3Me)Ph)	$COCH(Ph\text{-}4Me)_2$	CO_2H	0.51	-12

*IC_{50} (μM) for inhibition of ^{125}I-angiotensin II binding to rat adrenal receptor preparations.

**RHR = 2 kidney, 1-clip Goldblatt hypertensive rat.

TABLE II
ANTI HYPERTENSIVE ACTIVITY OF COMPOUNDS OF FORMULA II

EXAMPLE Number	R_1	R_5	X	Max % decrease in blood pressure 30 mg/kg PO in SHR*
158	H	Ph(4-SMe)	O	-17
155	H	Ph(4-OMe)	O	-39
157	H	Ph(2,4-$(OMe)_2$)	O	-22
154	H	iPr	O	-39
156	H	tBu	O	-18
162	H	iPr	S	-39
161	H	Ph	S	-28
159	H	Ph(4-OMe)	S	-39
160	H	Ph(4-NMe)$_2$	S	-34
129	3-CH_3	iPr	O	-36
130	1-CH_2Ph	iPr	O	-21
128	1-CH_2Ph	Ph(4-OMe)	S	-32
133	1-CH_2Ph	Ph(4-OMe)	O	-29
127	1-CH_2((4-OMe, 3Me)Ph)	Ph(4-OMe)	S	-24
273	1-CH_2((4-NO_2, 3Me)Ph)	Ph(4-OMe)	O	-14

*Spontaneously hypertensive rat

Accordingly, the present invention also includes a pharmaceutical composition for treating hypertension and a method for treating hypertension comprising administering to mammals, including humans, suffering therefrom either orally or parenterally the corresponding pharmaceutical composition. The composition contains a compound of the formula I' or the formula IIa each as defined above in appropriate unit dosage form.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders or tablet disintegrating agents; it can also be encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active compound. In the tablet the active compound is mixed with carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from 5 or 10 to about 70 percent of the active ingredient. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the

formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component (with or without other carriers) is surrounded by carrier, which is thus in association with it. Similarly, cachets are included. Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions. As an example may be mentioned water or water propylene glycol solutions for parenteral injection. Liquid preparations can also be formulated in solution in aqueous polyethylene glycol solution. Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, i.e., natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral

administration. Such liquid forms include solutions, suspensions, and emulsions. These particular solid form preparations are most conveniently provided in unit dose form and as such are used to provide a single liquid dosage unit. Alternately, sufficient solid may be provided so that after conversion to liquid form, multiple individual liquid doses may be obtained by measuring predetermined volumes of the liquid form preparation as with a syringe, teaspoon, or other volumetric container. When multiple liquid doses are so prepared, it is preferred to maintain the unused portion of said liquid doses at low temperature (i.e., under refrigeration) in order to retard possible decomposition. The solid form preparations intended to be converted to liquid form may contain, in addition to the active material, flavorants, colorants, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like. The liquid utilized for preparing the liquid form preparation may be water, isotonic water, ethanol, glycerine, propylene glycol, and the like as well as mixtures thereof. Naturally, the liquid utilized will be chosen with regard to the route of administration, for example, liquid preparations containing large amounts of ethanol are not suitable for parenteral use.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, for

example, packeted tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself or it can be the appropriate number of any of these in packaged form.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from 0.1 mg to 500 mg preferably to 1 to 100 mg according to the particular application and the potency of the active ingredient. The compositions can, if desired, also contain other compatible therapeutic agents.

In therapeutic use as described above, the mammalian dosage range for a 70 kg subject is from 0.1 to 150 mg/kg of body weight per day or preferably 1 to 100 mg/kg of body weight per day. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed.

Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The following Examples further illustrate the invention, but without, however, limiting it thereto.

The following examples specifically illustrate generally Methods A, B and C as described above.

METHOD A

EXAMPLE 1.

Methyl-1-(2-(1-adamantyl)ethyl)-5-diphenylacetyl)-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylate.

A solution of 11.8 mL trifluoromethanesulfonic anhydride in 70 mL dichloromethane is chilled to -70°C and treated dropwise with a solution composed of 12.6 g 1-adamantyl-2-hydroxyethane, 12.2 mL diisopropylethylamine and 70 mL dichloromethane. The solution is allowed to warm to -55°C over 45 min then a solution of 25 g N,1-bis-BOC-histidine methyl ester (J. Chem. Soc., Perkin Trans. I 1982; 1553-61.) in 70 mL dichloromethane is added dropwise. The reaction is then stirred at 25°C for 24 hr and poured into pH=7, 0.25 M potassium phosphate buffer (500 mL), stirring vigorously. The organic layer is separated, washed with the same buffer, dried and concentrated. 3-(2-(1-Adamantyl)ethyl)-N-BOC-histidine methyl ester is isolated by chromatography on silica gel (chloroform-methanol, 99:1) as a gum. NMR ($CDCl_3$) 3.85 (m,2H,NCH_2).

A portion of the above product (8.4 g) is treated with 350 mL 6N HCl, heating at reflux 2.5 hr. Evaporation gives 3-(2-(1-adamantyl)ethyl)histidine dihydrochloride as a glass. NMR (D_2O) 8.85 (s,1H,2-Im); 7.55 (s,1H,5-Im).

A solution of 7.8 g 3-(2-(1-adamantyl)ethyl)-histidine·2HCl in 100 mL 1N HCl is treated with 5 mL 36% formaldehyde, stirring 30 min at 25°C followed

by 90 min at reflux. Evaporation gives 1-(2-(1-adamantyl)ethyl)-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]-pyridine-6-carboxylic acid dihydrochloride as a white solid. NMR (D_2O) 8.90 (s,1H,2-Im).

A solution of 8.0 g of the above carboxylic acid in 350 mL methanol is treated with 35 mL trimethyl orthoformate, saturated with anhydrous HCl and heated at reflux 6 hr. The resulting solution is evaporated to a foam, suspended in 350 mL dichloromethane and treated dropwise with 350 mL cold 10% Na_2CO_3. The organic layer is separated, dried and evaporated to give methyl-1-(2-(1-adamantyl)ethyl)-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]-pyridine-6-carboxylate as a gum. NMR (D_2O+DCl) 4.08 (s,3H,CO_2Me).

A mixture of 1.1 g dicyclohexycarbodiimide, 1.10 g hydroxybenzotriazole hydrate, 1.1 g diphenylacetic acid and 25 mL acetonitrile is stirred at 25°C for 10 min then treated with a solution of 2.0 g methyl-1-(2-(1-adamantyl)ethyl)-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]-pyridine-6-carboxylate in 25 mL acetonitrile. The resulting suspension is stirred 48 hr at 25°C, filtered and the filtrate is evaporated, dissolved in dichloromethane, washed with 10% Na_2CO_3, dried and evaporated. Chromatography on silica gel (chloroform) gives a yield of methyl-1-(2-adamantyl)-ethyl)-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo-[4,5-c]-pyridine-6-carboxylate. NMR ($CDCl_3$) 3.63 (s,3H,CO_2Me), 5.35 (s,1H,$CHPh_2$).

EXAMPLE 2.

1-(2-(1-Adamantyl)ethyl)-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylic acid.

A solution of 2.0 g methyl-1-(2-(1-adamantyl)-ethyl)-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo-[4,5-c]-pyridine-6-carboxylate in tetrahydrofuran-methanol (3:1, 20 mL) is treated at 25°C with 4.1 mL 1N NaOH. After 6 hr the solution is evaporated, the residue is suspended in 10 mL water and treated with 4.1 mL 1N HCl. The resulting precipitate is collected by filtration and dried to afford a white solid, 1-(2-(1-adamantyl)ethyl)-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylic acid. MS (FAB) 524 (M+1). mp 168-175°C or 187° to 200°C dec.

EXAMPLE 3.

Methyl-1-(2-cyclohexylethyl)-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylate.

By substituting 2-cyclohexylethanol for 1-adamantyl-2-hydroxyethane in Example 1, one obtains this adduct. NMR ($CDCl_3$) 3.81 (t,2H,NCH_2).

EXAMPLE 4.

1-(2-Cyclohexylethyl)-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo[4.5-c]pyridine-6-carboxylic acid.

The methyl ester from Example 3 is saponified using the procedure described in Example 2 to give this acid as a white solid. MS (FAB) 472 (M+1). mp 137-140°C.

EXAMPLE 5.

Methyl-1-(2-phenylethyl)-5-phenylacetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylate.

By substituting 2-phenylethanol for 1-adamantyl-2-hydroxyethane and phenylacetic acid for diphenylacetic acid in Example 1, one obtains this adduct. NMR ($CDCl_3$) 4.08 (d of t,2H,NCH_2).

EXAMPLE 6.

1-(2-Phenylethyl)-5-phenylacetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylic acid.

The methyl ester from Example 5 is saponified using the procedure described in Example 2 to give this acid as a white solid. MS (DEI) 389 (M). mp 215-220°C.

In a process analogous to Examples 1 through 6 above and also as generally described in Method A above using appropriate starting materials the corresponding compounds of formula I are prepared.

EXAMPLE 7.

1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-1-(3-methylbutyl)-5-(phenylacetyl)-, (S)-; mp 168-171°C.

EXAMPLE 8.

1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 1-(2-cyclohexylethyl)-4,5,6,7-tetrahydro-5-(phenylacetyl)-, (S)- (R_1 is cyclohexylethyl); mp 200-205°C.

EXAMPLE 9.

1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-[bis(4-fluorophenyl)acetyl]-1-(2-cyclohexylethyl)-4,5,6,7-tetrahydro-, (S)-; mp 144-149°C.

EXAMPLE 10.

1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-(cyclohexylacetyl)-1-(2-cyclohexylethyl)-4,5,6,7-tetrahydro-, (S)-; MS (DEI) 401 (m).

EXAMPLE 11.

Methyl-1-(3-methyl-4-nitrophenyl)methyl-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]-pyridine-6-carboxylate.

A solution of 5.55 mL trifluoromethanesulfonic anhydride in 50 mL dichloromethane is chilled to -75°C and treated dropwise with a solution composed of 5.52 g 3-methyl-4-nitrobenzyl alcohol, 5.75 mL diisopropylethylamine and 50 mL dichloromethane. The resulting mixture is stirred 30 min at -75°C then treated dropwise with a solution of N,1-bis-BOC-histidine methyl ester[1] in 50 mL dichloromethane. The reaction mixture is allowed to warm to 25°C over 16 hr and poured into pH=7, 0.25 M potassium phosphate buffer (300 mL), stirring vigorously. Organic layer is washed with the same buffer, dried and concentrated. 3-(4-Methyl-3-nitrophenyl)methyl-n-BOC-histidine methyl ester is isolated by chromatography on silica gel (chloroform-methanol, 99:1) as a gum. NMR ($CDCl_3$) 2.55 (s,3H,ArMe); 1.34 (s,9H,t-Bu).

Hydrolysis of the above gum in refluxing 6N HCl affords 3-(3-methyl-4-nitrophenyl)methylhistidine dihydrochloride which is treated with formaldehyde and esterified as in Example 1 to give methyl-1-(3-methyl-4-nitrophenyl)methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylate as a solid. NMR ($CDCl_3$) 5.08 (s,2H,CH_2Ar).

A mixture of 16.7 g dicyclohexycarbodiimide, 10.9 g hydroxybenzotriazole hydrate, 17.2 g diphenylacetic acid and 150 mL acetonitrile is stirred at 25°C for 15 min then treated with a solution of 25.4 g methyl-1-(3-methyl-4-nitrophenyl)methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylate in 125 mL acetonitrile. The resulting suspension is stirred 48 hr at 25°C, filtered and the filtrate is evaporated, dissolved in dichloromethane, washed with 10% Na_2CO_3, dried and evaporated. Chromatography on silica gel (chloroform-methanol, 99:1) gives a crisp foam which crystallizes when triturated with methanol. MS (FAB) 525 (M+1).

EXAMPLE 12.

Methyl-1-(4-amino-3-methylphenyl)methyl-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]-pyridine-6-carboxylate.

A solution of 31.2 g methyl-1-(4-nitro-3-methylphenyl)methyl-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylate in tetrahydrofuran-methanol (2:1, 600 mL) is treated with 8.0 g Raney Nickel and placed under an atmosphere of hydrogen at 50 psi for 26 hr. The catalyst is removed by filtration and filtrate is evaporated to give a crisp foam. NMR ($CDCl_3$) 6.77 (s+d,2H,2,6-Ar); 6.60 (d,1H,5-Ar). mp 182-188°C.

EXAMPLE 13.

1-(4-Amino-3-methylphenyl)methyl-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylic acid.

The methyl ester from Example 12 is saponified using the procedure described in Example 2 to give this acid as a white solid. MS (FAB) 481 (M+1).

EXAMPLE 14.

Methyl-1-(4-dimethylamino-3-methylphenyl)-methyl-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo-[4,5-c]pyridine-6-carboxylate.

A solution of 2.9 g methyl-1-(4-amino-3-methylphenyl)methyl-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylate in 150 mL ethanol is treated consecutively with 2.5 mL 36% formaldehyde, 12 mL 1N HCl and 1.2 g $NaCNBH_3$. After 20 min addition of an additional 12 mL 1N HCl is begun via syringe pump over a 5 hr period. The reaction mixture is stirred an additional 1 hr then evaporated. The residue is partitioned between dichloromethane and 5% Na_2CO_3 (100 mL each) and the organic layer is dried and evaporated. The major product is isolated by chromatography on silica gel (chloroform-methanol, 99.5:0.5) as a crisp foam upon evaporation of solvents. NMR ($CDCl_3$) 2.67 (s,6H,$N(Me)_2$). mp 165°C.

EXAMPLE 15.

1-(4-Dimethylamino-3-methylphenyl)methyl-5-diphenyl-acetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]-pyridine-6-carboxylic acid.

The methyl ester from Example 14 is saponified using the procedure described in Example 2 to give this acid as a white solid. MS (FAB) 509 (M+1); 1017 (2M+1). mp 72-75°C.

EXAMPLE 16.

Ethyl-1-(2-hydroxyphenyl)methyl-5-diphenyl-acetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylate.

A solution of 8 g methanesulfonic anhydride in 45 mL dichloromethane is chilled to -50°C and treated dropwise with a solution of 6.2 mL 2-methoxybenzyl alcohol, 8.0 mL diisopropylethylamine and 45 mL dichloromethane. The resulting solution is warmed to 0°C over 30 min and treated dropwise with 15.0 g N,1-bis-BOC-histidine methyl ester dissolved in 45 mL dichloromethane. The mixture is then heated at reflux 24 hr, poured into 400 mL 0.25 M, pH=7 potassium phosphate buffer and the organic layer is separated, dried and evaporated. Chromatography on silica gel, eluting with chloroform-methanol (99:1) gives 3-(2-methoxyphenyl)methyl-N-BOC-histidine methyl ester as a gum. NMR ($CDCl_3$) 4.96 (s,2H,NCH_2Ar).

The above gum is treated with 150 mL 6N HCl at reflux for 3 hr, evaporated to a gum and triturated with ethanol to afford 3-(2-methoxyphenyl)methyl-histidine dihydrochloride as a colorless solid. MS (FAB) 267 (M+1); 551 (2M+1).

The above solid (3.7 g) is dissolved in 40 mL water and treated with 2.5 mL 36% formaldehyde, stirring 30 min at 25°C followed by 90 min at reflux. Evaporation gives a gum which is crystallized from ethanol-isopropanol to give 1-(2-methoxyphenyl)methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylic acid dihydrochloride as a colorless solid. NMR (D_2O) 3.95 (s,3H,OMe).

A solution of 2.85 g of the above carboxylic acid in concentrated HBr is heated at reflux 6 hr, diluted with 100 mL water and evaporated to afford 1-(2-hydroxyphenyl)methyl-4,5,6,7-tetrahydro-1H-imidazo-[4,5-c]pyridine-6-carboxylic acid dihydrobromide as an orange colored solid. NMR (D_2O) lacks the MeO singlet described above.

The crude acid is esterified by treatment with absolute ethanol and HCl at reflux. The ethanolic solution is concentrated and added dropwise to vigorously stirred ethyl acetate. Ethyl 1-(2-hydroxyphenyl)-methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylate hydrochloride hydrobromide is collected by filtration as an off-white, hygroscopic solid. NMR (D_2O) 1.33 (t,3H,CH_3).

A solution of the above ethyl ester, 3.8 mL diisopropylethylamine, 1.5 g imidazole and 60 mL acetonitrile is treated with 3.3 g t-butyldimethylsilyl chloride and stirred 7 hr at 25°C.

The reaction mixture is treated with 10 mL methanol, evaporated and partitioned between ethyl acetate and 10% Na_2CO_3. The organic layer is dried, evaporated and purified by chromatography on silica gel, eluting with chloroform-methanol (98:2) to give ethyl 1-(2-t-butyldimethylsiloxyphenyl)methyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylate as a gum. NMR ($CDCl_3$) 1.03 (s,9H,t-Bu).

A mixture of 1.3 g dicyclohexylcarbodiimide, 0.8 g hydroxybenzotriazole hydrate, 1.3 g diphenylacetic acid and 25 mL acetonitrile is stirred for 10 min then treated with a solution of the above

silyl ether (2.4 g) in 25 mL acetonitrile. The resulting suspension is stirred at 25°C 48 hr and filtered. The filtrate is evaporated, partitioned between dichloromethane and 10% Na_2CO_3 and the organic layer is dried and evaporated. Chromatography of the residue on silica gel, eluting with chloroform gives ethyl 1-(2-t-butyldimethylsiloxyphenyl)methyl-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]-pyridine-6-carboxylate as a gum. NMR ($CDCl_3$) 5.39 (s,1H,$COCHAr_2$).

The above compound is dissolved in 50 mL acetonitrile, treated with 0.65 mL 48% HF and stirred 6 hr at 25°C. The solution is then treated with 15.6 mL 1N NaOH, diluted with ethyl acetate and washed with saturated NaCl. Organic layer is dried, evaporated and chromatographed on silica gel ($CHCl_3$) to give ethyl 1-(2-hydroxyphenyl)methyl-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]-pyridine-6-carboxylate as a gum. NMR ($CDCl_3$) 9.68 (broad,1H,ArOH).

EXAMPLE 17.

1-(2-Hydroxyphenyl)methyl-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylic acid.

A solution of the product from Example 16 (2.35 g) in 25 mL THF-methanol (2:1) is treated with 10 mL 1N NaOH, stirring 90 min at 25°C. After treatment with 10 mL 1N HCl, the mixture is diluted with 60 mL methanol-water (2:1) and concentrated in vacuo until a thick slurry forms. The slurry is diluted with water and the desired carboxylic acid is collected by filtration. MS (FAB) 468 (M+1); mp 187-190°C.

EXAMPLE 18.

Methyl-1-(3-methyl-4-methoxyphenyl)methyl-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]-pyridine-6-carboxylate.

A solution of 10.8 g methanesulfonic anhydride in 120 mL dichloromethane is chilled to -50°C and treated dropwise with a solution of 9.4 g 3-methyl-4-methoxybenzyl alcohol, 10.8 mL diisopropylethylamine and 80 mL dichloromethane. The resulting solution is warmed to -25°C over 30 min and treated dropwise with 20.0 g N,1-bis-BOC-histidine methyl ester dissolved in 125 mL dichloromethane. The mixture is then allowed to warm to 25°C over 4 hr, stirring at this temperature 24 hr. The reaction mixture is poured into 700 mL 0.25 M, pH = 7 potassium phosphate buffer and the organic layer is separated, dried and evaporated. Chromatography on silica gel, eluting with chloroform-methanol (99:1) gives 3-(3-methyl-4-methoxyphenyl)methyl-N-BOC-histidine methyl ester as a gum. NMR ($CDCl_3$) 1.43 (s,9H,t-Bu).

The remainder of the synthesis proceeds as described in Example 1, using the appropriate quantities of reagents to afford methyl 1-(3-methyl-4-methoxyphenyl)methyl-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylate as a gum. NMR ($CDCl_3$) 4.91 (d,2H,CH_2Ar).

EXAMPLE 19.

1-(3-Methyl-4-methoxyphenyl)methyl-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]-pyridine-6-carboxylic acid.

The ester product from Example 18 is converted to this acid using the procedure described in Example 2. MS (FAB) 496 (M+1); mp 222-225°C.

EXAMPLE 20.

Methyl-1-(4-trifluoromethylphenyl)methyl-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]-pyridine-6-carboxylate.

Substitution of 4-trifluoromethylbenzyl alcohol for 3-methyl-4-nitrobenzyl alcohol in Example 11 gives this product. NMR ($CDCl_3$) 5.06 (s,2H,CH_2Ar).

EXAMPLE 21.

1-(4-Trifluoromethylphenyl)methyl-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylic acid.

Hydrolysis of the ester from Example 20 according to the procedure given in Example 2 affords this acid. MS (FAB) 520 (M+1).

EXAMPLE 22.

(S)-5-[bis(4-chlorophenyl)acetyl]-4,5,6,7-tetrahydro-1-(phenylmethyl)-1H-imidazo[4,5-c]pyridine-6-carboxylic acid.

To 1.3 g of dicyclohexylcarbodiimide in 20 mL of acetonitrile is added 1.7 g of bis-(4-chlorophenyl) acetic acid followed by 0.8 g of 1-hydroxybenzotriazole hydrate. This mixture is stirred 20 min at room temperature at which point 2.0 g of the dihydrochloride salt of 1-benzylspinacine methyl ester is added followed by 2.0 mL of triethylamine. This mixture is stirred for 2 hr at room

temperature, filtered, concentrated and diluted with ethyl acetate. The solution is washed twice with water and once with saturated sodium bicarbonate, dried, filtered and concentrated. The resulting oil is chromotographed on silica gel eluting with 10% acetone in chloroform to afford 1.60 g (52%) of the desired amide ester, R_f = 0.35 (10% acetone/chloroform).

This amide ester is then diluted in 10 mL of tetrahydrofuran and 3.0 mL of an aqueous 1 M sodium hydroxide solution is added. After stirring for 3 hr at room temperature, 3.0 mL of an aqueous 1 M hydrogen chloride solution is added. The solution is concentrated and the residue is triturated with water. The solid is collected by filtration and dried to afford 1.30 g of the (S)-5-[bis(4-chlorophenyl)acetyl]-4,5,6,7-tetrahydro-1-(phenylmethyl)-1H-imidazo[4,5-c]pyridine-6-carboxylic acid product, mp 162-170°C.

EXAMPLE 23.

(S)-5-[bis(4-fluorophenyl)acetyl]-4,5,6,7-tetrahydro-1-(phenylmethyl)-1H-imidazo[4,5-c]pyridine-6-carboxylic acid.

This compound is prepared following the procedure of Example 22 and using bis-(4-fluorophenyl)acetic acid as starting material. The product is a white solid with $[\alpha]_D^{20}$ = 11.3° (0.96%, methanol).

EXAMPLE 24.

(S)-5-(cyclopentylphenylacetyl)-4,5,6,7-tetrahydro-1-[(4-methoxy-3-methylphenyl)methyl]-1H-imidazo-[4,5-c]pyridine-6-carboxylic acid.

This compound is prepared following the procedure of Example 22 and using cyclopentyl phenyl acetic acid as starting material. The product has mp 190°C (dec).

EXAMPLE 25.

(S)-[bis(4-methylphenyl)acetyl]-4,5,6,7-tetrahydro-1-[(4-methoxy-3-methylphenyl)methyl]-1H-imidazo[4,5-c]-pyridine-6-carboxylic acid.

This compound is prepared following the procedure of Example 22 and using bis-(4-methylphenyl)acetic acid as staring material. The product is a white solid with $[\alpha]_D^{20} = 4.9^\circ$ (1.09%, methanol).

EXAMPLE 26.

(S)-5-(cyclohexylacetyl)-4,5,6,7-tetrahydro-1-[(4-methoxy-3-methylphenyl)methyl]-1H-imidazo-[4,5-c]-pyridine-6-carboxylic acid.

This compound is prepared following the procedure of Example 22 and using cyclohexylacetic acid as starting material. The product is a white solid, m/e = 426.1 (FAB).

EXAMPLE 27.

5-[(9H-Fluoren-9-yl)carbonyl]-4,5,6,7-tetrahydro-1-(phenylmethyl)-1H-imidazo[4,5-c]pyridine-6-carboxylic acid.

A solution of 2.3 g of fluorene-9-carbonyl chloride in acetonitrile (25 mL) is added slowly to a solution of I base, 2.7 g of l-benzylspinacine methyl ester; the methyl ester of the compound of Example 152 hereinafter, 1.5 g of triethyl amine and acetonitrile (25 mL) at room temperature. After 1 hr the separated triethylamine hydrochloride is filtered and the filtrate is concentrated at reduced pressure to remove solvent. Water (50 mL) is added to the residue and the insoluble gum is extracted with ethyl acetate (100 mL). The solution is dried (Na_2SO_4) and concentrated to give the methyl ester of the title product. This material is hydrolyzed directly.

The ester is dissolved in methanol (50 mL). 1N-Sodium hydroxide (20 mL) is added and the solution is maintained at reflux for 10 min. 1N-Hydrochloric acid (20 mL) is added to precipitate the product. Recrystallization from dimethylformamide-water gives a pure sample, mp 229-231°C.

In a process analogous to Examples 11 through 27 above and also as generally described in Method A above using appropriate starting materials the corresponding compounds of formula I are prepared as follows:

EXAMPLE 28.

1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-5-[(methylphenylamino)carbonyl]-1-(phenylmethyl)-; mp 173-180°C.

EXAMPLE 29.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-[(9H-fluoren-9-yl)carbonyl]-4,5,6,7-tetrahydro-1-(phenylmethyl)-, (±)-; mp 229-231°C.

EXAMPLE 30.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-(diphenylacetyl)-4,5,6,7-tetrahydro-1-(phenylmethyl)-, (S)-; mp 220-225°C (dec).

EXAMPLE 31.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-5-(phenylacetyl)-1-(phenylmethyl)-, (S)-; mp 215-217.5°C (dec).

EXAMPLE 32.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-5-[(4-methoxyphenyl)acetyl]-1-(phenylmethyl)-, monohydrochloride, (S)-; mp 195°C (dec).

EXAMPLE 33.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-5-[(3-methoxyphenyl)acetyl]-1-(phenylmethyl)-, monohydrochloride, (S)-; mp 182°C (dec).

EXAMPLE 34.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-1-(phenylmethyl)-5-[(3,4,5-trimethoxyphenyl)-acetyl]-, (S)-; mp 146-146.5°C.

EXAMPLE 35.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-[(3,4-dichlorophenyl)acetyl]-4,5,6,7-tetrahydro-1-(phenylmethyl)-, (S)-; mp 222-226°C.

EXAMPLE 36.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-5-[(4-nitrophenyl)acetyl]-1-(phenylmethyl)-, (S)-; mp 270-272°C.

EXAMPLE 37.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-5-[(4-hydroxy-3-nitrophenyl)acetyl]-1-phenylmethyl)-, (S)-; mp 243-245°C.

EXAMPLE 38.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-1-(phenylmethyl)-5-[[(4-(trifluoromethyl)-phenyl]acetyl]-, (S)-; mp 243-245°C (dec).

EXAMPLE 39.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-[(4-aminophenyl)acetyl]-4,5,6,7-tetrahydro-1-(phenylmethyl)-, dihydrochloride, (S)-; mp 260-265°C.

EXAMPLE 40.
1H-Imidazo[4,5-c]pyridine-5,6-carboxylic acid, 4,5,6,7-tetrahydro-1-(phenylmethyl)-, 5-phenylmethyl ester, (S)-; mp 208-210°C (dec).

EXAMPLE 41.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-5-(oxophenylacetyl)-1-(phenylmethyl)-, (S)-; MS (DEI) 389 (m).

EXAMPLE 42.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-5-[(2-methoxyphenyl)acetyl]-1-(phenylmethyl)-, (S)-; mp 122-135°C.

EXAMPLE 43.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-5-[(2-hydroxyphenyl)acetyl]-1-(phenylmethyl)-, (S)-; mp 150-166°C (dec).

EXAMPLE 44.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-1-(phenylmethyl)-5-(3-pyridinylacetyl)-; mp 237-238°C.

EXAMPLE 45.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-(cyclohexylacetyl)-4,5,6,7-tetrahydro-1-(phenylmethyl)-, (S)-; mp 162-175°C.

EXAMPLE 46.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-1-(phenylmethyl)-5-(9H-xanthen-9-ylcarbonyl)-; mp 256-258°C.

EXAMPLE 47.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-5-(1H-indol-3-ylacetyl)-1-(phenylmethyl)-; mp 237-240°C.

EXAMPLE 48.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-5-(1-naphthalenylacetyl)-1-(phenylmethyl)-, (S)-; MS (DEI) 425 (m).

EXAMPLE 49.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-5-(1-oxo-3,3-diphenylpropyl)-1-(phenylmethyl)-, (S)-; MS (DEI) 465 (m).

EXAMPLE 50.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetra-5-(1H-inden-3-ylcarbonyl)-1-(phenylmethyl)-; mp 213-215°C (dec).

EXAMPLE 51.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-[bis(4-methoxyphenyl)acetyl]-4,5,6,7-tetrahydro-1-(phenylmethyl)-, (S)-; NMR (DMSO-d_6) 3.66 (s,3H,OMe); 3.69 (s,3H,OMe).

EXAMPLE 52.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-[bis(4-methylphenyl)acetyl]-4,5,6,7-tetrahydro-1-(phenylmethyl)-, (S)-; NMR (DMSO-d_6) 2.21 (s,3H,Me); 2.18 (s,3H,Me).

EXAMPLE 53.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-5-[[(4-methoxyphenyl)amino]carbonyl]-, (±)-; mp 225-230°C.

EXAMPLE 54.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-[bis(4-nitrophenyl)acetyl]-4,5,6,7tetrahydro-1-(phenylmethyl)-, (S)-; mp 154-158°C.

EXAMPLE 55.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-[bis(4-aminophenyl)acetyl]-4,5,6,7-tetrahydro-1-(phenylmethyl)-, (S)-; MS (FAB) 482 (m+1).

EXAMPLE 56.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-1-[(4-methoxy-3-methylphenyl)methyl]-5-(phenylacetyl)-, (S)-; mp 239-240°C.

EXAMPLE 57.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-[bis(4-fluorophenyl)acetyl]-4,5,6,7-tetrahydro-1-[(4-methoxy-3-methylphenyl)methyl]-, (S)-; NMR (DMSO-d_6) 2.07 (s,3H,Me).

EXAMPLE 58.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-1-[(4-methoxy-3-methylphenyl)methyl]-5-(1-oxo-3-phenyl-3-propenyl)-, [S-(E)]-; mp 249-257°C.

EXAMPLE 59.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-1-[(4-methoxy-3-methylphenyl)methyl]-5-[[(methoxyphenyl)amino]carbonyl]-, (S)-; mp 175-177°C.

EXAMPLE 60.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-1-[(4-methoxy-3-methylphenyl)methyl]-5-[(methylphenylamino)carbonyl]-, (S)-; MS (FAB) 435 (m+1).

EXAMPLE 61.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-[bis(4-methoxyphenyl)acetyl]-4,5,6,7-tetrahydro-1-[(4-methoxy-3-methylphenyl)methyl]-, (S)-; NMR (DMSO-d_6) 2.07 (s,3H,Me).

EXAMPLE 62.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-1-[(4-methoxy-3-methoxyphenyl)methyl]-5-(9H-xanthen-9-ylcarbonyl)-, (S)-; mp 255-262°C.

EXAMPLE 63.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-(9H-fluoren-9-ylcarbonyl)-4,5,6,7-tetrahydro-1-[(4-methoxy-3-methylphenyl)methyl]-, (S)-; mp 200-205°C.

EXAMPLE 64.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-1-[(4-methoxy-3-methylphenyl)methyl]-5-(1-oxo-3,3-diphenylpropyl)-, (S)-; MS (FAB) 1019 (2m+1); 510 (m+1).

EXAMPLE 65.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-1-[(4-methoxy-3-methylphenyl)methyl]-5-(2-thienylacetyl)-, (S)-; mp 235-237°C.

EXAMPLE 66.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-1-[(4-methoxy-3-methylphenyl)methyl]-5-(3-thienylacetyl)-, (S)-; mp 236-238°C.

EXAMPLE 67.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-1-[(4-methoxy-3-methylphenyl)methyl]-5-(oxo-2-thienylacetyl)-, (S)-; mp 172-180°C.

EXAMPLE 68.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-[bis(4-nitrophenyl)acetyl]-4,5,6,7-tetrahydro-1-[(4-methoxy-3-methylphenyl)methyl]-, (S)-; mp 152-158°C.

EXAMPLE 69.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-[bis(4-chlorophenyl)acetyl]-4,5,6,7-tetrahydro-1-[(4-methoxy-3-methylphenyl)methyl]-, (S)-; mp 145-154°C.

EXAMPLE 70.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-(cyclohexylphenylacetyl)-4,5,6,7-tetrahydro-1-[(4-methoxy-3-methylphenyl)methyl]-; mp 140-149°C.

EXAMPLE 71.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-(diphenylacetyl)-4,5,6,7-tetrahydro-1-[(4-hydroxy-3-methylphenyl)-methyl]-, (S)-; mp 217-225°C.

EXAMPLE 72.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-(diphenylacetyl)-4,5,6,7-tetrahydro-1-[(3-methyl-4-nitrophenyl)-methyl]-, (S)-; mp 158-165°C.

EXAMPLE 73.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 1-[(3,4-dimethylphenyl)methyl]-5-(diphenylacetyl]-4,5,6,7-tetrahydro-, (S)-; mp 238-240°C.

EXAMPLE 74.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-(diphenylacetyl)-4,5,6,7-tetrahydro-1-[(3-methyl-phenyl)methyl]-, methyl ester, monohydrochloride, (S)-; mp 130-135°C.

EXAMPLE 75.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-(diphenylacetyl)-4,5,6,7-tetrahydro-1-[(3-methyl-phenyl)methyl]-, (S)-; mp 134-145°C.

EXAMPLE 76.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-(diphenylacetyl)-4,5,6,7-tetrahydro-1-[(3-methyl-4-nitrophenyl)-methyl]-, methyl ester, (S)-; mp 168-171°C.

EXAMPLE 77.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-1-[(4-hydroxyphenyl)methyl]-6-(phenylacetyl)-, (S)-; mp 208-212°C.

EXAMPLE 78.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-(diphenylacetyl)-4,5,6,7-tetrahydro-1-[(4-methoxyphenyl)methyl]-, (S)-; mp 150-160°C.

EXAMPLE 79.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-1-[(4-methoxyphenyl)methyl]-5-(phenylacetyl)-, (S)-; mp 228-230°C.

EXAMPLE 80.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-(diphenylacetyl)-4,5,6,7-tetrahydro-1-[(4-nitrophenyl)methyl]-, (S)-; mp 210-215°C.

EXAMPLE 91.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 1-[(4-aminophenyl)methyl]-5-(diphenylacetyl)-4,5,6,7-tetrahydro-, (S)-; Lot P: mp 129-131°C, Lot Q: mp 214-216°C (dec).

EXAMPLE 82.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 1-[[(4-(acetylamino)phenyl]methyl]-5-(diphenylacetyl)-4,5,6,7-tetrahydro-, (S)-; mp 254-256°C.

EXAMPLE 83.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-(diphenylacetyl)-4,5,6,7-tetrahydro-1-[2-methoxyphenyl)methyl]-, (S)-; mp 148-153°C.

EXAMPLE 84.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 1-[[(4-(dimethylamino)phenyl]methyl]-5-(diphenylacetyl)-4,5,6,7-tetrahydro-; mp 166-170°C.

EXAMPLE 85.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 1-[[(4-(dimethylamino)phenyl]methyl]-5-(diphenylacetyl)-4,5,6,7-tetrahydro-, dihydrobromide; MS (DEI) 494 (m).

EXAMPLE 86.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 1-[(3,4-dimethylphenyl)methyl]-5-(diphenylacetyl]-4,5,6,7-tetrahydro, (S)-; mp 238-240°C.

EXAMPLE 87.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-[bis-(4-fluorophenyl)acetyl]-4,5,6,7-tetrahydro-1-[(3-methyl-4-nitrophenyl)methyl], (S)-; mp 155-165°C.

EXAMPLE 88.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 1-[(4-amino-3-methylphenyl)methyl]-5-(cyclohexylphenylacetyl)-4,5,6,7-tetrahydro, (6S)-; mp 159-164°C.

EXAMPLE 89.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 1-[(4-amino-3-methylphenyl)methyl]-5-[bis(4-fluorophenyl)-acetyl]-4,5,6,7-tetrahydro-, (S)-; mp 198-204°C.

EXAMPLE 90.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-(diphenylacetyl)-1-[(4-fluorophenyl)methyl]-4,5,6,7-tetrahydro-; mp 158-162°C.

EXAMPLE 91.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-[(2,3-dihydro-1H-inden-1-yl)carbonyl]-4,5,6,7-tetrahydro-1-[(4-methoxy-3-methylphenyl)methyl]-, (6S)-; mp 247-249°C.

EXAMPLE 92.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 1-[[(4-(dimethylamino)phenyl]methyl]-5-(diphenylacetyl)-4,5,6,7-tetrahydro-; NMR ($CDCl_3$) 1.14 (m,6H,2Me).

EXAMPLE 93.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-5-methyl-1-[(3-methyl-4-nitrophenyl)methyl]-, methyl ester, (S)-; mp 103-106°C.

EXAMPLE 94.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-[bis-(4-fluorophenyl)acetyl]-1-[[4-(dimethylamino)-3-methyl-phenyl]methyl]-4,5,6,7-tetrahydro-, (S)-; mp 178-182°C.

EXAMPLE 95.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 1-[[(4-(acetylamino)-3-methylphenyl]methyl]-5-(diphenylacetyl)-4,5,6,7-tetrahydro-, (S)-; mp 175-180°C.

EXAMPLE 96.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-(diphenylacetyl)-4,5,6,7-tetrahydro-1-[[(3-methyl-4-[[(methylamino)carbonyl]amino]phenyl]methyl]-, (S)-; mp 198-201°C.

EXAMPLE 97.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 1-[[(4-(benzoylamino)-3-methylphenyl]methyl]-5-(diphenylacetyl)-, (S)-; mp 178-185°C.

EXAMPLE 98.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-[bis-(4-chlorophenyl)acetyl]-1-[[4-(dimethylamino)-3-methylphenyl]methyl]-4,5,6,7-tetrahydro-, (R)-; mp 243-246°C (dec).

EXAMPLE 99.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 1-[[(4-(dimethylamino)-3-methylphenyl]methyl]-5-(diphenylacetyl)-4,5,6,7-tetrahydro-, (R)-; mp 255-256°C (dec).

EXAMPLE 100.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-(diphenylacetyl)-4,5,6,7-tetrahydro-1-[(4-methoxy-3-nitrophenyl)methyl]-, (S)-; NMR (DMSO-d_6) 3.93 (s,3H).

EXAMPLE 101.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-(diphenylacetyl)-4,5,6,7-tetrahydro-1-[(4-methoxy-3-methyl-5-nitrophenyl)methyl]-, (S)-; mp 195-199°C.

EXAMPLE 102.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-1-[(4-methoxy-3-methylphenyl)methyl]-5-(1-oxo-2-phenylpropyl)-; mp 223°C (dec).

EXAMPLE 103.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-(diphenylacetyl)-1-[(3-ethyl-4-methoxyphenyl)methyl]-4,5,6,7-tetrahydro-; mp 137-146°C.

EXAMPLE 104.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-1-[(4-methoxy-3-methylphenyl)methyl]-5-(tricyclo[3.3.1.$1^{3,7}$]dec-1-ylacetyl)-, (S)-; mp 210°C (dec).

EXAMPLE 105.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-1-[(4-methoxy-3-methylphenyl)methyl]-5-(1-oxo-2,2-diphenylpropyl)-, (S)-; mp 210°C (dec).

EXAMPLE 106.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-1-[(4-methoxy-3-methylphenyl)methyl]-5-[(1-phenylcyclohexyl)carbonyl]-, (S)-; mp 145°C (dec).

EXAMPLE 107.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-1-[(4-methoxy-3-methylphenyl)methyl]-5-[(1-phenylcyclopentyl)carbonyl]-, (S)-; mp 195°C (dec).

EXAMPLE 108.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-[(4-chlorophenyl)phenylacetyl]-1-[[4-(dimethylamino)-3-methylphenyl]methyl]-4,5,6,7-tetrahydro-; mp 170-190°C.

EXAMPLE 109.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-[(2-chlorophenyl)(4-chlorophenyl)acetyl]-1-[[4-(dimethylamino)-3-methylphenyl]methyl]-4,5,6,7-tetrahydro-, (S)-; mp 175-185°C.

EXAMPLE 110.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 1-[(3,5-dibromo-4-methoxyphenyl)methyl]-5-(diphenylacetyl)-4,5,6,7-tetrahydro-, (S)-; mp 152-157°C.

EXAMPLE 111.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-[(4-chlorophenyl)(4-methylphenyl)acetyl]-1-[[4-(dimethylamino)-3-methylphenyl]methyl]-4,5,6,7-tetrahydro-; mp 170-180°C.

EXAMPLE 112.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-(diphenylacetyl)-4,5,6,7-tetrahydro-1-[[3-methyl-4[(3-methyl-1-oxobutyl)amino]phenyl]methyl]-, (S), methyl ester; MS (DEI) 578 (m).

EXAMPLE 113.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-[(3-chlorophenyl)phenylacetyl]-1-[[4-(dimethylamino)3-methylphenyl]methyl]-4,5,6,7-tetrahydro-; mp 155-165°C.

EXAMPLE 114.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-(diphenylacetyl)-4,5,6,7-tetrahydro-1-[[3-methyl-4-[[[(1-methylethyl)amino]carbonyl]amino]phenyl]-methyl]-, (S)-; MS (FAB) 1131 (2m+1); 566 (m+1).

EXAMPLE 115.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-(diphenylacetyl)-4,5,6,7-tetrahydro-1-[[3-methyl-4-[(3-methyl-1-oxobutyl)amino]phenyl]methyl]-, (S)-; MS (DEI) 564 (m).

EXAMPLE 116.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 1-[(4-amino-3-methylphenyl)methyl]-5-[(3-chlorophenyl)-phenylacetyl]-4,5,6,7-tetrahydro-; mp 145-160°C.

EXAMPLE 117.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 1-[(4-amino-3-bromo-5-methylphenyl)methyl]-5-(diphenyl-acetyl)-4,5,6,7-tetrahydro-, (S)-; mp 225-228°C.

EXAMPLE 118.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 1-[(4-amino-3-methylphenyl)methyl]-5-[bis(4-chlorophenyl)-acetyl]-4,5,6,7-tetrahydro-, (S)-; mp 240-250°C (dec).

EXAMPLE 119.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-[bis-(4-chlorophenyl)acetyl]-1-[[4-(dimethylamino)-3-methylphenyl]methyl]-4,5,6,7-tetrahydro-, (S)-; mp 160-170°C.

EXAMPLE 120.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 1-[(4-amino-3-bromo-5-methylphenyl)methyl]-5-(diphenylacetyl)-4,5,6,7-tetrahydro-, methyl ester; MS (DEI) 574 (m+1).

EXAMPLE 121.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 1-[(4-amino-3-methylphenyl)methyl]-4,5,6,7-tetrahydro-5-[(3-methylphenyl)phenylacetyl]-; mp 165-175°C.

EXAMPLE 122.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 1-[[(4-(dimethylamino)-3-methylphenyl]methyl]-4,5,6,7-tetrahydro-5-[(3-methylphenyl)phenylacetyl]-; mp 200-210°C (dec).

EXAMPLE 123.
4,5,6,7-Tetrahydro-5-(2-phenylethyl)-1-(phenylmethyl)-1H-imidazo[4,5-c]pyridine-6-carboxylic acid, dihydrochloride.

Freshly dried molecular sieves (3 Å, 7.0 g) are added to a solution of 1-benzylspinacine dihydrochloride (3.4 g), 1.2 g phenylacetaldehyde and ethanol (50 mL). Triethylamine (2.0 g) is added and the mixture is stirred for 1 hr at room temperature. Bromocresol green (ca 0.10 mg) and sodium cyanoborohydride

(1.3 g) are added. Ethanolic-hydrogen chloride is then added until color became light green over the course of 1 hr. After stirring two days at room temperature, ether (50 mL) is added and excess hydrogen chloride gas is passed in. When gas evolution ceases, the sieves and solids are filtered and the intermediate ester hydrochloride is precipitated with ether (300 mL) as a gum. The free base is prepared by treating a water (20 mL) solution of the hydrochloride with excess sodium bicarbonate and extraction into ethyl acetate; wt 1.2 g.

A solution of crude ester (1.1 g), methanol (20 mL) and 1N sodium hydroxide (10 mL) is heated at reflux for 10 min and concentrated to remove the methanol. 1N Hydrochloric acid (10 mL) is added to precipitate the product as a gum. The aqueous portion is decanted and the remaining water is azeotroped by two successive additions and removed of absolute ethanol (50 mL). The remaining gum is dissolved in absolute ethanol (10 mL), filtered and treated with excess ethanolic hydrogen chloride (10 mL). Concentration gave the product which is recrystallized from ethanol-ether to give 0.10 g of the product as the dihydrochloride; mp 200-205°C.

EXAMPLE 124.

4,5,6,7-Tetrahydro-1,5-bis(phenylmethyl)-1H-imidazo-[4,5-c]pyridine-6-carboxylic acid, methyl ester.

A solution of 2.0 g of 1-benzylspinacine, 20 mL of acetonitrile, 0.8 g of 1-methylamine and 1.3 g of benzyl bromide is allowed to stand at room temperature for four days. The solvent is removed, water (10 mL)

is added and the product is extracted with ethyl acetate (10 mL) and ether (100 mL). Concentration gives the product which upon crystal-lization from ethyl acetate (8 mL) and petroleum ether gives a pure sample; mp 91-93°C.

EXAMPLE 125.

4,5,6,7-Tetrahydro-5-[(methylphenylamino)carbonyl]-1-(phenylmethyl)-1H-imidazo[4,5-c]pyridine-6-carboxylic acid.

A solution of 1.0 g of the ester of Example 124, methanol (10 mL) and 1N sodium hydroxide (4.0 mL) is heated at reflux for 15 min. The methanol is removed and 2N hydrochloric acid (2.0 mL) is added to precipitate the product. Recrystallization from methanol gave a pure product; mp 220-222°C.

The following Examples 126 through 134 illustrate preparation of selected compounds of formula II, using examples of Method A above for the preparation of intermediates:

EXAMPLE 126.

1,4,6,7,8a,9-Hexahydro-7-phenyl-1-(phenylmethyl)-6-thioxo-8H-diimidazo[1,5-a:5'-d]pyridine-8-one.

Phenyl isothiocyanate (1.4 g) is added to a stirred mixture of 2.9 g of 1-benzylspinacine in dimethylformamide. The resulting solution is allowed to stand at room temperature for 15 min. Water (20 mL) is added to precipitate the product. Recrystallization from methanol gives 3.1 g; mp 224-226°C.

EXAMPLE 127.

6,7,8a,9-Tetrahydro-1-[(4-methoxy-3-methylphenyl)-methyl]-7-(4-methoxyphenyl)-6-thioxo-1H-diimidazo-[1,5-a:4',5'-d]-pyridine-8(4H)-one.

A solution of 1.7 g of 1-(4-methoxy-3-methyl)-benzylspinacine methyl ester, dimethylformamide (4 mL) and 4-methoxyphenylisothiocyanate (0.9 g) is heated on a steam bath for 15 min. Water (20 mL) is decanted and the residue is triturated with water. The resulting solid is filtered and washed with water. A crystalline hydrochloride salt was prepared as follows. The base was dissolved in warm (40°) 2-propanol (20 mL). Upon addition of concentrated hydrochloric acid (1.0 mL) product separated. Recrystallization from methanol-ether gave 1.40 g of pure product; mp 250-265°C.

EXAMPLE 128.

6,7,8a,9-Tetrahydro-7-(4-methoxyphenyl)-1-(phenylmethyl)-6-thioxo-1H-diimidazo[1,5-a:4',5'-d]pyridine-8(4H)-one.

A solution of 1.4 g of 1-benzylspinacine methyl ester, dimethylformamide (4 mL) and 4-methoxyphenyl-isothiocyanate (0.9 g) is heated on the steam bath for 15 min. Water (50 mL) is added to precipitate 2.5 g of a yellow solid. This is purified by precipitation from aqueous methanol to give 6,7,8a,9-tetrahydro-7-(4-methoxyphenyl)-1-(phenylmethyl)-6-thioxo-1H-diimidazo[1,5-a:4',5'-d]pyridine-8(4H)-one; mp 100-120°C.

EXAMPLE 129.

(S)-8a,9-dihydro-3-methyl-7-(1-methylethyl)-3H-diimidazo-[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione.

Intermediate 3-methylspinacine dihydrochloride was prepared from 3-methyl-L-histidine (Vega Biochemical) by the method of Example 164 hereinafter.

A solution of 1-methylspinacine dihydrochloride (1.40 g) in 1N sodium hydroxide (16.5 mL, 0.0165 mole) and tetrahydrofuran (20 mL) is cooled to 5°C. Isopropylisocyanate (0.65 g) in tetrahydrofuran (5 mL) is added with stirring. After 1 hr at room temperature the THF is distilled and the aqueous solution is clarified. Concentrated hydrochloric acid (10 mL) is added. The solution is heated on the steam bath for 15 min and concentrated to dryness at reduced pressure. Water (5 mL) and solid potassium carbonate, to saturate, are added and the separated product is extracted into methylene chloride. Removal of solvent gives product. Recrystallization from ethyl acetate-petroleum ether gives the pure product, mp 161-164°C.

EXAMPLE 130.

8a,9-Dihydro-7-(1-methylethyl)-1-(phenylmethyl)-1H-diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione hydrobromide.

This compound is prepared following the procedure of Example 129, however, the acid used in the cyclization step was hydrobromic acid, the product had mp 196-198°C.

In a process analogous to the above Examples 126 through 129 and also as generally described in Method A above using appropriate starting materials the corresponding compounds of formula I are prepared as follows:

EXAMPLE 131.
3H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-3-methyl-7-phenyl-; mp 199-202°C.

EXAMPLE 132.
1H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-1-methyl-7-(1-methylethyl)-; mp 134-137°C.

EXAMPLE 133.
1H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-7-(4-methoxyphenyl)-1-(phenylmethyl)-, monohydrochloride; mp 181-187°C.

EXAMPLE 134.
1H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-1-[(4-methoxy-3-methylphenyl)methyl]-7-(4-methoxyphenyl)-, monohydrochloride, (S)-; mp 154-159°C.

METHOD B

EXAMPLE 135.
Methyl-5-diphenylacetyl-3-(2-oxo-2-phenylethyl)-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylate.

A suspension of 12.1 g histidine methyl ester dihydrochloride in 150 mL chloroform is treated at 0°C with excess anhydrous ammonia. The resulting suspension is filtered and the filtrate is evaporated to give histidine methyl ester as an oil. This oil is dissolved in 100 mL dichloromethane and added dropwise to a refluxing solution of 8.1 g carbonyl diimidazole in 100 mL dichloromethane. Refluxing is continued 15 min after addition is complete then the reaction mixture is concentrated until it begins to crystallize. Ethyl ether is added and the solid is collected by filtration. Recrystallization from acetonitrile gives methyl-5,6,7,8-tetrahydro-5-oxo-imidazo[1,5-c]-pyrimidine-7-carboxylate; mp 159-164°C.

A mixture of 7.8 g of the above product, 8.0 g phenacyl bromide and 200 mL acetonitrile is heated at reflux 6 hr. The cooled suspension is filtered, rinsing with acetonitrile to afford 7-methoxycarbonyl-2-(2-oxo-2-phenylethyl)-5,6,7,8-tetrahydro-5-oxo-imidazo-[1,5-c]pyrimidinium bromide; mp 223-224°C (decomposes with gas evolution).

The above imidazolium salt is treated with 250 mL 6N HCl at reflux for 4 hr and evaporated to a gum. This gum is dissolved in 500 mL ethanol, concentrated to a syrup and added dropwise to vigorously stirred ethyl acetate to give 3-(2-oxo-2-phenylethyl)-histidine as a hygroscopic mixture of hydrochloride and hydrobromide salts. MS (FAB) 274 (M+1).

A solution of 33 g 3-(2-oxo-2-phenylethyl)-histidine dihydrohalide in 400 mL 1N HCl is treated with 17.5 mL 36% formaldehyde, stirring 30 min at

25°C followed by 2 hr at reflux. Evaporation gives a gum which crystallizes upon standing. Trituration with ethanol affords 3-(2-oxo-2-phenylethyl)-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridine-6-carboxylic acid as a mixture of hydrochloride and hydrobromide salts. MS (FAB) 286 (M+1).

The above carboxylic acid is converted to its methyl ester by dissolution in 400 mL methanol and treatment with 50 mL trimethyl orthoformate. The resulting solution is saturated with HCl and heated at reflux 6 hr. Upon cooling, the resulting slurry is concentrated to approximately 200 mL and filtered to give methyl-3-(2-oxo-2-phenylethyl)-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridine-6-carboxylate dihydrochloride as a white solid. MS (FAB) 300 (M+1).

A mixture of 9.3 g dicyclohexycarbodiimide, 6.1 g hydroxybenzotriazole hydrate, 9.5 g diphenylacetic acid and 100 mL acetonitrile is stirred at 25°C for 15 min (suspension A). A mixture of 15.8 g methyl-3-(2-oxo-2-phenylethyl)-4,5,6,7-tetrahydro-3H-imidazo-[4,5-c]pyridine-6-carboxylate dihydrochloride, 14.8 mL diisopropylethylamine and 100 mL acetonitrile is stirred 10 min at 25°C then treated with suspension A, using 100 mL acetonitrile to complete the transfer. The resulting suspension is stirred 48 hr, filtered and the filtrate is evaporated, dissolved in dichloromethane, washed with 10% Na_2CO_3, dried and evaporated. Chromatography on silica gel (chloroform-methanol, 99:1) gives methyl-5-diphenylacetyl-3-(2-oxo-2-phenylethyl)-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylate as foam. MS (FAB) 494 (M+1).

EXAMPLE 136.

Methyl-1-(3,4-dimethoxyphenyl)methyl-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylate.

A solution of 1.5 g 3,4-dimethoxybenzyl chloride, 2.5 g methyl-5-diphenylacetyl-3-(2-oxo-2-phenylethyl)-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylate and 30 mL acetonitrile is heated at reflux 16 hr. The cooled solution is added dropwise to 400 mL vigorously stirred ether and the resulting precipitate is collected by filtration. This precipitate is dissolved in 40 mL methanol and treated with 8 g zinc dust and 40 mL acetic acid. The resulting suspension is sonicated 2 hr then the solution is filtered from excess zinc. The filtrate is dissolved in 400 mL dichloromethane and treated dropwise with 450 mL 10% Na_2CO_3 with vigorous stirring. The organic phase is separated, dried, concentrated and the major product is isolated by chromatography on silica gel (chloroform-methanol, 99:1) as a crisp foam. NMR ($CDCl_3$) 3.88 (s,3H,OMe); 3.80 (s,3H,OMe); 3.58 (s,3H,OMe).

EXAMPLE 137.

1-(3,4-Dimethoxyphenyl)methyl-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylic acid.

The methyl ester from Example 136 is saponified using the procedure described in Example 2 to give this acid as a white solid. MS (FAB) 512 (M+1).

EXAMPLE 138.

Methyl-1-(3-trifluoromethylphenyl)methyl-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylate.

A solution of 1.4 g 3-trifluoromethylbenzyl chloride, 3.0 g methyl-5-diphenylacetyl-3-(2-oxo-2-phenylethyl)-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]-pyridine-6-carboxylate and 20 mL acetonitrile is heated at reflux 16 hr. An additional 1.4 mL 3-trifluoromethylbenzyl chloride is added and refluxing continued 24 hr. The cooled solution is added dropwise to 400 mL vigorously stirred ether and the resulting precipitate is collected by filtration. This precipitate is dissolved in 60 mL methanol and treated with 10 g zinc dust and 60 mL acetic acid. The resulting suspension is sonicated 2 hr then the solution is filtered from excess zinc. The filtrate is dissolved in 400 mL dichloromethane and treated dropwise with 520 mL 10% Na_2CO_3 with vigorous stirring. The organic phase is separated, dried, concentrated and the major product is isolated by chromatography on silica gel (chloroform-methanol, 99.5:0.5) as a crisp foam. NMR ($CDCl_3$) 5.05 (s,2H,NCH_2Ar).

EXAMPLE 139.

1-(3-Trifluoromethylphenyl)methyl-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylic acid.

The methyl ester from Example 138 is saponified using the procedure described in Example 2 to give this acid as a white solid. MS (FAB) 520 (M+1); 1039 (2M+1).

EXAMPLE 140.

Methyl-1-(3-methylphenyl)methyl-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylate.

A solution of 2.7 mL 3-methylbenzyl bromide, 5.0 g methyl-5-diphenylacetyl-3-(2-oxo-2-phenylethyl)-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylate and 50 mL acetonitrile is heated at reflux 4 hr. The cooled solution is added dropwise to 750 mL vigorously stirred ether and the resulting precipitate is collected by filtration. This precipitate is dissolved in 75 mL methanol and treated with 16 g zinc dust and 75 mL acetic acid. The resulting suspension is sonicated 6 hr then the solution is filtered from excess zinc. The filtrate is dissolved in 400 mL dichloromethane and treated dropwise with 650 mL 10% Na_2CO_3 with vigorous stirring. The organic phase is separated, dried, concentrated and the major product is isolated by chromatography on silica gel (chloroform-methanol, 99.5:0.5) as a crisp foam. NMR ($CDCl_3$) 4.97 (s,2H,NCH_2Ar).

EXAMPLE 141.

1-(3-Methylphenylmethyl-5-diphenylacetyl-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylic acid.

The methyl ester from Example 140 is saponified using the procedure described in Example 2 to give this acid as a white solid. MS (DEI) 465 (M).

In a process analogous to the above Examples 135 through 141 and also as generally described in Method B above using appropriate starting materials the corresponding compounds of formula I are prepared as follows:

EXAMPLE 142.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-(diphenylacetyl)-4,5,6,7-tetrahydro-1-(phenylmethyl)-, (S)-; mp 220-225°C (dec).

EXAMPLE 143.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-(diphenylacetyl)-4,5,6,7-tetrahydro-1-[(3-methoxyphenyl)methyl]-, (S)-; mp 138-150°C.

EXAMPLE 144.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-(diphenylacetyl)-1-(diphenylmethyl)-4,5,6,7-tetrahydro-, (S)-; mp 157-163°C.

EXAMPLE 145.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-(diphenylacetyl)-4,5,6,7-tetrahydro-1-[(2-methoxy-5-methylphenyl)methyl]-, (S)-; mp 135-154°C.

EXAMPLE 146.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 1-[(3-bromophenyl)methyl]-5-(diphenylacetyl)-4,5,6,7-tetrahydro-, (S)-; mp 195-215°C.

EXAMPLE 147.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 1-[(3-(chlorophenyl)methyl]-5-(diphenylacetyl)-4,5,6,7-tetrahydro-, (S)-; mp 137-152°C.

EXAMPLE 148.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-(diphenylacetyl)-4,5,6,7-tetrahydro-1-(2-naphthalenylmethyl)-, (S)-; mp 180°C (dec).

EXAMPLE 149.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 1-(3-bromo-4-methoxyphenyl)methyl-5-(diphenylacetyl)-4,5,6,7-tetrahydro-, (S)-; mp 150-165°C.

METHOD C

EXAMPLE 150.
(S)-4,5,6,7-tetrahydro-3H-imidazo[4,5-c]pyridine-6-carboxylic acid, methyl ester, dihydrochloride, 0.33 mole hydrate; (spinacine, methyl ester).

A mixture of 82 g of spinacine hydrochloride and methanol (2.5 L) is saturated with hydrogen chloride. The mixture is heated at reflux with stirring overnight. The resulting solution, at reflux, is again treated with a stream of hydrogen chloride for 1 hr and concentrated to half volume. Addition of ether (0.5 L) gives 92.60 g of product. Recrystallization from methanol-ether gives pure product containing 0.33 mole of water, mp 140-160°; $[\alpha]_D^{23}$ -79.6°C (1.08%, methanol).

EXAMPLE 151.

(S)-8a,9-dihydro-7-phenyl-3H-diimidazo[1,5-a:4',5'-d]-pyridine-6,8-(4H,7H)-dione, 0.75 mole hydrate.

Phenylisocyanate (5.95 g) is added to a slurry of spinacine methyl ester dihydrochloride (12.7 g) dimethylformamide (150 mL) and triethylamine (15.2 g). After the mild exotherm (40°C) the mixture is stirred at room temperature for 2 hr. The triethylamine hydrochloride is filtered and the filtrate is concentrated at reduced pressure. Water (200 mL) is added to the residue to give crude product. Recrystallization from methanol-water gives 9.8 g of II containing 0.75 mole water, mp 133-136°C; $[\alpha]_D^{23}$ -201.3°C (1.05%, methanol).

EXAMPLE 152.

8a,9-Dihydro-7-phenyl-1-(phenylmethyl)-1H-diimidazo-[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione isomer A.

A solution of 27.3 g of the compound of Example 151 in 20% tetramethylammonium hydroxide-in-methanol (46.5 g) and dimethylformamide (60 mL) is treated with benzyl bromide (17.4 g). After 1/2 hr the separated solids are filtered, washed with dimethylformamide (50 mL) and then with water (200 mL) to give isomer A. Recrystallization from dimethylformamide gave 9.2 g of pure product, mp 277-279°C.

Isomer B, 8a,9-dihydro-7-phenyl-3-(phenylmethyl)-1H-diimidazo-[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione is isolated by precipitation with water from the above reaction filtrate. Purification of B is affected by trituration of the crude with acetone, filtration of solids, concentration of the acetone

filtrate and recrystallization of the residue from dimethylformamide; mp 227-229°C.

EXAMPLE 153.

1-(Phenylmethyl)-4,5,6,7-tetrahydro-1H-imidazo-[4,5-c]-pyridine-6-carboxylic acid, dihydrochloride; (also known as 1-benzyl-spinacine).

A solution of 9.0 g of the Isomer A compound of Example 152 in a solution of potassium hydroxide (18.0 g), water (13 mL) and methanol (40 mL) is maintained at reflux for 6 hr. The methanol is distilled at reduced pressure, water (15 mL) is added and the mixture is heated on the steam bath to dissolve clumps of solid. The cooled solution is extracted with ether (150 mL). Ice is added to the aqueous phase and concentrated hydrochloric acid (ca. 30 mL) is cautiously added to pH 2. This solution is passed through a cation exchange resin (ca. 200 g; Bio-Rad AGW50) and the column is washed with ca. three column volumes of water to remove inorganic salts. The product is removed from the column by passage of concentrated ammonium hydroxide (200 mL) and then water (250 mL). The ammonia fractions are concentrated at reduced pressure to give 6.0 g of the amorphous amino acid. The dihydrochloride salt is prepared as follows: a solution of 6.0 g of the above amino acid in water (5 mL) is treated with concentrated hydrochloric acid (5 mL). 2-Propanol (25 mL) is added and the mixture is filtered and washed with 2-propanol (10 mL) and ether to give product. Recrystallization from water gives a pure sample, mp 280-282°C, dec.

EXAMPLE 154.
8a,9-Dihydro-7-(1-methylethyl)-3H-diimidazo-[1,5-a:4',5'-d]-pyridine-6,8(4H,7H)-dione.

This compound is prepared following the procedure of EXAMPLE 151 above using isopropyl isocyanate as the starting material. mp 149-157°C.

EXAMPLE 155.
8a,9-Dihydro-7-(4-methoxyphenyl)-1H-diimidazo-[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione.

This compound (mp 142-140°C) is prepared following the procedure of Example 151 above above using 4-methoxy-phenylisocyanate as the starting material. mp 142-148°C.

EXAMPLE 156.
7-(1,1-Dimethylethyl)-8a,9-dihydro-1H-diimidazo-[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione.

This compound is prepared following the procedure of Example 151 above using t-butyl isocyanate as starting material. The product has mp 156-158°C.

EXAMPLE 157.
7-(2,4-Dimethoxyphenyl)-8a,9-dihydro-1H-diimidazo-[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione.

This compound is prepared following the procedure of Example 151 above using 2,4-dimethoxyphenylisocyanate as starting material. The product has mp 241-243°C (dec).

EXAMPLE 158.
8a,9-Dihydro-7-[4-(methylthio)phenyl]-1H-diimidazo-[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione.

This compound is prepared by the procedure of Example 151 above using 4-(methylthio)phenylisocyanate as the starting material; the product has mp 241-243°C (dec).

EXAMPLE 159.

1,4,6,7,8a,9-Hexahydro-7-(4-methoxyphenyl)-6-thioxo-8H-diimidazo[1,5-a:4',5'-d]pyridine-8-one.

A mixture of 10.0 g of spinacine hydrochloride, dioxane (250 mL) and triethylamine (5.00 g) is stirred at room temperature for 15 min. p-Methoxyphenylisothiocyanate (8.15 g) is added and the mixture is maintained at reflux under nitrogen for 24 hr. After filtration the solution is concentrated to give 18.77 g of product. Purification by silica gel chromatography gives 10.9 g of pure product, mp 266.5-270°C (dec).

EXAMPLE 160.

7-[4-(Dimethylamino)phenyl]-1,4,6,7,8a,9-hexahydro-6-thioxo-8H-diimidazo[1,5-a:4',5'-d]pyridine-8-one.

This compound is prepared by the procedure of Example 159 above, using 4-(dimethylamino)phenylisothiocyanate as starting material. The product has mp 185-200°C.

EXAMPLE 161.

1,4,6,7,8a,9-Hexahydro-7-phenyl-6-thioxo-8H-diimidazo-[1,5-a:4',5'-d]pyridine-8-one.

This compound is prepared following the procedure of Example 159 above and using phenylisothiocyanate as starting material. The product has mp 142-143°C (dec).

EXAMPLE 162.

1,4,6,7,8a,9-Hexahydro-7-(1-methylethyl)-6-thioxo-8H-diimidazo-(1,5-a:4',5'-d]pyridine-8-one.

This compound is prepared following the procedure of Example 159 above using isopropylisothiocyanate as starting material. The product has mp 218-220°C (dec).

EXAMPLE 163.

(S)-3-(phenylmethyl)-4,5,6,7-tetrahydro-1H-imidazo-[4,5-c]pyridine-6-carboxylic acid, dihydrochloride, 1.5 moles hydrate; (3-benzylspinacine).

A solution of 24.5 g of im-benzylhistidine, concentrated hydrochloric acid (200 mL) and dimethoxymethane (60 mL) is allowed to stand at room temperature overnight. Additional dimethoxymethane (60 mL) is added and the solution is heated on a steam bath for 3 hr. Volatiles are removed at 55°C and reduced pressure. The residue is dissolved in warm water (20 mL). 2-Propanol (250 mL) is added to precipitate the product. Recrystallization from water-2-propanol gives pure product, mp 130-135°C; $[\alpha]_D^{23}$ -72.8°C (c = 1.12%, methanol).

EXAMPLE 164.

(S)-5-benzoyl-4,5,6,7-tetrahydro-3-(phenylmethyl)-3H-imidazo[4,5-c]pyridine-6-carboxylic acid.

A solution of 3-benzylspinacine, 2 HCl, 1.5 H_2O (1.79 g) in 1N sodium hydroxide (20 mL) and dioxane (30 mL) is cooled to 3°C. With stirring a solution of benzoyl chloride (0.70 g) in dioxane (3 mL) is added dropwise over 5 min. The ice bath is removed and, after 1 hr at room temperature,

glacial acetic acid (ca. 0.5 g) is added to precipitate crude product. This is filtered and washed with water and ether to remove traces of benzoic acid. Recrystallization is accomplished by dissolution in methanol (5 mL), addition of water (20 mL) and removal of methanol by distillation to give pure product; mp 233-235°C; $[\alpha]_D^{23}$ -11.4°C (1.12%, 0.1 N NaOH).

EXAMPLE 165.

8a,9-Dihydro-7-(4-methoxyphenyl)-1-(phenylmethyl)-1H-diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, hydrochloride.

This compound is prepared following the procedure for Example 151 above using 4-methoxyphenylisocyanate as starting material. The product has mp 181-187°C.

EXAMPLE 166.

8a,9-Dihydro-1-[(4-methoxy-3-methylphenyl)methyl]-7-(4-methoxyphenyl)-]H-diimidazo[1,5-a:4',5'-d]pyridine-6,8-(4H,7H)-dione.

This compound is prepared following the procedure of Example 151 above and using 1-(4-nitro-3-methyl)benzyl-spinacine and 4-methoxyphenylisocyanate as starting materials. The product has mp 154-159°C; $[\alpha]_D^{23}$ -104.9°C (1.03, methanol).

EXAMPLE 167.

4,5,6,7-Tetrahydro-1-[(4-methoxy-3-methylphenyl)methyl]-5-[[(4-methoxyphenyl)amino]carbonyl]-1H-imidazo[4,5-c]-pyridine-6-carboxylic acid.

A mixture of 7.5 g of 1-(4-methoxy-3-methyl)-benzylspinacine hydrochloride, 1N-sodium hydroxide (60 mL) and tetrahydrofuran (20 mL) is cooled with

stirring to 5°C. p-Methoxyphenylisocyanate (2.98 g) is added. After 10 min in the ice bath the mixture is stirred 1 hr at room temperature. The tetrahydrofuran is distilled at reduced pressure and solids are filtered. The clear filtrate is cooled in an ice bath and 1N hydrochloric acid (20 mL) is added to precipitate a solid. This is filtered, washed with water and added to methanol (50 mL) whereupon crystals separated. Filtration gave product. Recrystallization from methanol-methylene chloride gives pure product, mp 175-177°C dec; $[\alpha]_D^{23}$ +40.0°C (1.35% 50:50 methanol-chloroform).

EXAMPLE 168.

5-(Diphenylacetyl)-4,5,6,7-tetrahydro-1-(phenylmethyl)-, 1H-imidazo[4,5-c]pyridine-6-carboxylic acid, methyl ester.

A solution of 2.0 g 1-benzylspinacine methyl ester in acetonitrile (25 mL) and 0.84 g triethylamine is cooled to 10°C with stirring. A solution of 1.78 g diphenylacetyl chloride in acetonitrile (5 mL) is added slowly, keeping the temperature below 20°C with cooling. After 1/2 hr at room temperature most of the acetonitrile is distilled at reduced pressure and ethyl acetate (50 mL), ether (50 mL) and ice water (50 mL) are added. The aqueous layer is separated and the organic layer is washed successively with water (50 mL) and 2% sodium bicarbonate solution (50 mL). The dried ($MgSO_4$) organic phase is charcoaled, filtered and concentrated to give 3.2 g of crude product. Crystallization from ethyl acetate-petroleum ether gives 1.6 g of the title compound, mp 127-129°C; NMR ($CDCl_3$) 3.49 (s,3H,OMe).

EXAMPLE 169.

5-(Diphenylacetyl)-4,5,6,7-tetrahydro-1-(phenylmethyl)-1H-imidazo[4,5-c]pyridine-6-carboxylic acid.

A solution of 1.2 g of the methyl ester of Example 168 above in methanol (10 mL) and 5.2 mL 1N sodium hydroxide is heated at reflux for 5 min. The methanol is distilled and water (30 mL) is added to the residue. The clear solution is treated with 1N hydrochloric acid to precipitate the product. Recrystallization from methanol-ether gives 0.8 g of a pure sample, mp 167-169°C.

In a process analogous to the above Examples 151-169 and also as generally described in part by Method C above using appropriate starting materials the corresponding compounds of formula II are prepared as follows:

EXAMPLE 170.

8H-Diimidazo[1,5-a:4',5'-d]pyridine-8-one, 1,4,6,7,8a,9-hexahydro-7-(4-nitrophenyl)-6-thioxo; mp 215-216°C (dec).

EXAMPLE 171.

8H-Diimidazo[1,5-a:4',5'-d]pyridine-8-one, 1,4,6,7,8a,9-hexahydro-7-propyl-6-thioxo-; mp 85-105°C.

EXAMPLE 172.

8H-Diimidazo[1,5-a:4',5'-d]pyridine-8-one, 7-[4-ethoxy-phenyl)-1,4,6,7,8a,9-hexahydro-6-thioxo-; mp 144-145°C (dec).

EXAMPLE 173.
8H-Diimidazo[1,5-a:4',5'-d]pyridine-8-one, 7-ethyl-1,4,6,7,8a,9-hexahydro-6-thioxo-; NMR ($CDCl_3$) 1.23 (t,3H,Me).

EXAMPLE 174.
1H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-, monohydrochloride, (S)-; mp 315-325°C.

EXAMPLE 175.
3H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 7-(2,6-dichlorophenyl)-8a,9-dihydro-, monohydrochloride (±)-; mp 345-347°C.

EXAMPLE 176.
1H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 7-(4-chlorophenyl)-8a,9-dihydro-; MS (DEI) 303 (m+1).

EXAMPLE 177.
1H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 7-cyclohexyl-8a,9-dihydro-; MS (DEI) 274 (m).

EXAMPLE 178.
1H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-7-[3-(trifluoromethyl)phenyl]-; MS (DEI) 336 (m).

EXAMPLE 179.
1H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-7-(2-methoxyphenyl)-; mp 102-104°C (dec).

EXAMPLE 180.
1H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-7-(2-naphthalenyl)-; mp 158-162°C.

EXAMPLE 181.
1H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-7-[4-(1-methylethyl)phenyl]-; mp 100-106°C (dec).

EXAMPLE 182.
1H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-7-[4-(methylsulfonyl)phenyl]-; mp 197-207°C (dec).

EXAMPLE 183.
Benzoic acid, 4-(4,8,8a,9-tetrahydro-6,8-dioxo-1H-diimidazo[1,5-a:4',5'-d]pyridine-7(6H)-yl)-, ethyl ester; mp 115-150°C.

EXAMPLE 184.
1H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-7-(4-phenoxyphenyl)-; mp 110-130°C.

EXAMPLE 185.
3H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-7-(1-methylethyl)-, monohydrobromide; mp 273-274°C.

EXAMPLE 186.
1H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-7-(3,4,5-trimethoxyphenyl)-; mp 157-159°C.

EXAMPLE 187.
1H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 7-(2-chloro-6-methoxyphenyl)-8a,9-dihydro-; mp 250-254°C (dec).

EXAMPLE 188.
1H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-7-(3-methoxyphenyl)-; mp 157-161.5°C.

EXAMPLE 189.
1H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 7-(3,5-dimethoxyphenyl)-8a,9-dihydro-; mp 237.5-240°C (dec).

EXAMPLE 190.
3H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-7-(phenylmethyl)-, monohydrochloride, (S)-; mp 260-270°C.

EXAMPLE 191.
1H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 7-(3,4-dichlorophenyl)-8a,9-dihydro-; mp 135-150°C dec.

EXAMPLE 192.
1H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-7-(4-hydroxyphenyl)-; mp 271-273°C (dec).

EXAMPLE 193.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-[(3,4-dichlorophenyl)acetyl]-4,5,6,7-tetrahydro-1-(phenylmethyl)-, (S)-; mp 222-226°C.

EXAMPLE 194.
1H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 7-(2,6-dimethylphenyl)-8a,9-dihydro-; MS (DEI) 296 (m).

EXAMPLE 195.
1H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 7-(4-aminophenyl)-8a,9-dihydro-; mp 233-243°C (dec).

EXAMPLE 196.
1H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 7-(4-butoxyphenyl)-8a,9-dihydro-; mp 174-175°C.

EXAMPLE 197.
8H-Diimidazo[1,5-a:4',5'-d]pyridine-8-one, 7-(2-furanyl-methyl)-1,4,6,7,8a,9-hexahydro-6-thioxo-, monohydro-bromide; mp 195°C (dec).

EXAMPLE 198.
1H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-7-phenyl-1-(phenylmethyl)-, (±)-; mp 277-279°C.

EXAMPLE 199.
1H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-7-phenyl-1-(2-propenyl)-; mp 204-206°C.

EXAMPLE 200.
1H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 1-[(4-fluorophenyl)methyl]-8a,9-dihydro-7-phenyl-; mp 205-206.5°C (dec).

EXAMPLE 201.
1H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-1-[(4-methylphenyl)methyl]-7-phenyl-; mp 249-253°C.

EXAMPLE 202.
1H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-7-phenyl-1-(3-phenylpropyl)-; mp 168-169°C.

EXAMPLE 203.
1H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-7-[(4-methylthio)phenyl]-1-(phenylmethyl)-; mp 202-203°C.

EXAMPLE 204.
1H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-3-(phenylmethyl)-7-[3-(trifluoromethyl)-phenyl]-; mp 171-172.5°C.

EXAMPLE 205.
1H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-1-[(4-nitrophenyl)methyl]-7-phenyl-; mp 90°C.

EXAMPLE 206.
1H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-7-(2-naphthalenyl)-1-(phenylmethyl)-; mp 235-238°C.

EXAMPLE 207.
1H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-7-[4-(1-methylethyl)phenyl]-1-(phenylmethyl)-; mp 220-223°C (dec).

EXAMPLE 208.
3H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-3-(phenylmethyl)-, (S)-; mp 230-235°C.

EXAMPLE 209.
3H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 3-[(3-chlorophenyl)methyl]-8a,9-dihydro-7-phenyl-; mp 217-225°C.

EXAMPLE 210.
3H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-3-[(4-nitrophenyl)methyl]-7-phenyl-; mp 240-244.

EXAMPLE 211.
3H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 3-[(4-fluorophenyl)methyl]-8a,9-dihydro-7-phenyl-; mp 242-243°C (dec).

EXAMPLE 212.
3H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 7-(4-chlorophenyl)-8a,9-dihydro-3-(phenylmethyl)-; mp 183-184°C.

EXAMPLE 213.
3H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-3-[(4-methylphenyl)methyl]-7-phenyl-; mp 215-219°C.

EXAMPLE 214.
3H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-3-[(3-methoxyphenyl)methyl]-7-phenyl-; mp 204-205°C.

EXAMPLE 215.
3H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-7-[4-(methylthio)phenyl]-3-(phenylmethyl)-; mp 226-228°C.

EXAMPLE 216.
3H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-7-phenyl-3-(3-phenylpropyl)-; mp 117-118°C.

EXAMPLE 217.
3H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 7-cyclohexyl-8a,9-dihydro-3-(phenylmethyl)-; MS (DEI) 364 (m).

EXAMPLE 218.
3H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-7-[4-(methylsulfonyl)phenyl]-3-(phenylmethyl)-; mp 184-190°C (dec).

EXAMPLE 219.
1H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-1-(phenylmethyl)-7-[3-(trifluoromethyl)-phenyl]-; mp 227-230°C (dec).

EXAMPLE 220.
3H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-7-(2-naphthalenyl)-3-(phenylmethyl)-; mp 232-234°C.

EXAMPLE 221.
3H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-7-[4-(1-methylethyl)phenyl]-3-(phenylmethyl)-; mp 228-229°C (dec).

EXAMPLE 222.
3H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-7-(1-methylethyl)-3-(phenylmethyl)-, monohydrochloride; mp 246-248°C.

EXAMPLE 223.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-5-[(phenylamino)carbonyl]-1-(phenylmethyl), (±)-; mp 270-280°C.

EXAMPLE 224.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-[[(4-fluorophenyl)amino]carbonyl]-4,5,6,7-tetrahydro-1-(phenylmethyl)-; mp 209-213°C.

EXAMPLE 225.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-5-[[(4-nitrophenyl)amino]carbonyl]-1-(phenyl-methyl)-; mp 192-194°C (dec).

EXAMPLE 226.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-5-[[(4-methylphenyl)amino]carbonyl]-1-(phenyl-methyl)-; mp 227-235°C.

EXAMPLE 227.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-[[[(1,1'-biphenyl]-2-ylamino)carbonyl]-4,5,6,7-tetrahydro-1-(phenylmethyl)-; mp 158-162°C (dec).

EXAMPLE 228.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-[[[4-(ethoxycarbonyl)phenyl]amino]carbonyl]-4,5,6,7-tetrahydro-1-(phenylmethyl)-; mp 173-175°C (dec).

EXAMPLE 229.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-1-[(4-methylphenyl)methyl]-5-[(phenylamino)-carbonyl]-; NMR (DMSO-d_6) 2.27 (s,3H,Me).

EXAMPLE 230.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-5-[[[4-(methylthio)phenyl]amino]carbonyl]-1-(phenylmethyl)-; mp 201-202°C.

EXAMPLE 231.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-[[(4-chlorophenyl)amino]carbonyl]-4,5,6,7-tetrahydro-1-(phenylmethyl)-; mp 203-204°C (dec).

EXAMPLE 232.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-5-[[[4-(methylsulfonyl)phenyl]amino]carbonyl]-1-(phenylmethyl)-; mp 225-226.5°C (dec).

EXAMPLE 233.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-1-(phenylmethyl)-5-[[[3-(trifluoromethyl)-phenyl]amino]carbonyl]-; mp 228-231°C (dec).

EXAMPLE 234.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-1-[(4-nitrophenyl)methyl]-5-[(phenylamino)-carbonyl]-, monosodium salt; mp 160-163°C (dec).

EXAMPLE 235.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-5-[[(1-methylethyl)amino]carbonyl]-1-(phenyl-methyl)-; mp 170-180°C (dec).

EXAMPLE 236.
3H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-[[(1,1-dimethylethyl)amino]carbonyl]-4,5,6,7-tetrahydro-3-(phenylmethyl)-, (S)-; mp 151-154°C.

EXAMPLE 237.
3H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-5-[(phenylamino)carbonyl]-3-(phenylmethyl)-; mp 222-227°C (dec).

EXAMPLE 238.
3H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-[[(2,6-dimethylphenyl)amino]carbonyl]-4,5,6,7-tetrahydro-3-(phenylmethyl)-, (S)-; mp 145-150°C.

EXAMPLE 239.
3H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-3-methyl-5-[(phenylamino)carbonyl]-; mp 176-178°C (dec).

EXAMPLE 240.
3H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-[[(4-chlorophenyl)amino]carbonyl]-4,5,6,7-tetrahydro-3-(phenylmethyl)-; mp 179-182°C (dec).

EXAMPLE 241.
3H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-5-[[[4-(methylthio)phenyl]amino]carbonyl]-3-(phenylmethyl)-; mp 220-224°C (dec).

EXAMPLE 242.
3H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-[(cyclohexylamino)carbonyl]-4,5,6,7-tetrahydro-3-(phenylmethyl)-, monosodium salt; mp 182-184.5°C (dec).

EXAMPLE 243.
3H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-5-[[[4-(methylsulfonyl)phenyl]amino]-carbonyl]-3-(phenylmethyl)-; mp 180-181°C (dec).

EXAMPLE 244.

3H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-3-[(4-nitrophenyl)methyl]-5-[(phenylamino)-carbonyl]-; mp 240-242°C (dec).

EXAMPLE 245.

3H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-5-[[(1-methylethyl)amino]carbonyl]-3-(phenylmethyl)-; mp 188-190°C (dec).

EXAMPLE 246.

1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-benzoyl-4,5,6,7-tetrahydro-1-(phenylmethyl)-; mp 236-238°C.

EXAMPLE 247.

5H-Imidazo[4,5-c]pyridine-5,6-dicarboxylic acid, 1,4,6,7-tetrahydro-1-(phenylmethyl)-, 5-phenylmethyl ester; mp 123-127°C.

EXAMPLE 248.

1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-5-(phenylacetyl)-1-(phenylmethyl)-; mp 221-223°C.

EXAMPLE 249.

1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-5-[(methylphenylamino)carbonyl]-1-(phenyl-methyl)-; mp 192-195°C (dec).

EXAMPLE 250.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-5-[(methylphenylamino)carbonyl]-1-(phenylmethyl)-, monohydrochloride; mp 204-206°C (dec).

EXAMPLE 251.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-5-(1-oxo-3-phenyl-2-propenyl)-1-(phenylmethyl)-; mp 242-244°C.

EXAMPLE 252.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-1-(phenylmethyl)-5-(phenoxyacetyl)-; mp 205-208°C.

EXAMPLE 253.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-acetyl-4,5,6,7-tetrahydro-1-(phenylmethyl)-; mp 225-227°C.

EXAMPLE 254.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-5-[[methyl(2-phenylethyl)amino]carbonyl]-1-(phenylmethyl)-; mp 134-136°C.

EXAMPLE 255.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-5-[[methyl(phenylmethyl)amino]carbonyl]-1-(phenylmethyl)-; mp 172-174°C (dec).

EXAMPLE 256.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-5-(1-oxo-3-phenylpropyl)-1-(phenylmethyl)-; mp 205-207°C.

EXAMPLE 257.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-[(ethylphenylamino)carbonyl]-4,5,6,7-tetrahydro-1-(phenylmethyl)-; mp 207-209°C.

EXAMPLE 258.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-1-(phenylmethyl)-5-[(phenylmethyl)sulfonyl]-; mp 190-192°C.

EXAMPLE 259.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-1-(phenylmethyl)-5-[(phenoxyacetyl)-; mp 205-208°C.

EXAMPLE 260.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-1-(phenylmethyl)-5-[(phenylmethyl)sulfonyl]-, methyl ester, (S)-; mp 129-131°C.

EXAMPLE 261.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-5-(2-methyl-1-oxo-3-phenyl-2-propenyl)-1-(phenylmethyl)-; mp 190-192°C.

EXAMPLE 262.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-5-[(4-methylphenyl)sulfonyl]-1-(phenylmethyl)-, (±)-; mp 259-261°C.

EXAMPLE 263.

5H-Imidazo[4,5-c]pyridine-5-butanoic acid, 1,4,6,7-tetrahydro-6-(methoxycarbonyl)-4-oxo-1-(phenylmethyl)-, methyl ester, (S)-; mp 125-127°C.

EXAMPLE 264.

1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-5-(1-oxo-2,3-diphenyl-2-propenyl)-1-(phenylmethyl)-, [S-(E)]-; mp 225-230°C.

EXAMPLE 265.

3H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-acetyl-4,5,6,7-tetrahydro-3-(phenylmethyl)-, methyl ester, (S)-; mp 155-157°C.

EXAMPLE 266.

3H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 5-acetyl-4,5,6,7-tetrahydro-3-(phenylmethyl)-, (S)-; mp 120-160°C.

EXAMPLE 267.

5H-Imidazo[4,5-c]pyridine-5,6-dicarboxylic acid, 3,4,6,7-tetrahydro-3-(phenylmethyl)-, 5-phenyl ester; mp 174-177°C (dec).

EXAMPLE 268.

3H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-5-(1-oxo-3-phenyl-2-propenyl)-3-(phenylmethyl)-, monohydrochloride; mp 254-256°C.

Finally, Examples are hereinafter provided to illustrate processes to prepare the additional compounds of formula I and II.

EXAMPLE 269.

2-Benzoyl-8a,9-dihydro-7-(1-methylethyl)--(phenylmethyl)-1H-diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione.

Trimethylamine (2.09 g) is added to a solution of 0.7 g of the compound of Example 55, dimethylformamide (50 mL) and benzoyl chloride (2.90 g). After 24 hr at room temperature water is added dropwise until turbidity develops. The separated crystals are filtered and washed with methanol (10 mL) and water to give a pale yellow solid. Recrystallization from methanol-methylene chloride gives 3.50 g of pure product; mp 215-217°C.

EXAMPLE 270.

3H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 2-benzoyl-8a,9-dihydro-7-phenyl-; mp 213-215°C.

EXAMPLE 271.

3H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-2-(4-nitrobenzoyl)-7-phenyl-3-(phenylmethyl)-; mp 230-232°C.

EXAMPLE 272.

3H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-2-(4-methoxybenzoyl)-7-phenyl-3-(phenylmethyl)-; mp 200-201°C.

EXAMPLE 273.
1H-Diimidazo[1,5-c:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-7-(4-methoxyphenyl)-1-[(3-methyl-4-nitrophenyl)methyl], monohydrochloride; mp 258-261°C (dec).

EXAMPLE 274.
2-Benzoyl-4,5,6,7-tetrahydro-5-[[(1-methylethyl)amino]-carbonyl]-1-(phenylmethyl)-1H-imidazo[4,5-c]pyridine-6-carboxylic acid.

A suspension of 0.5 g of the product from Example 269, methanol (50 mL) and 1N sodium hydroxide (10 mL) is heated on a steam bath for 15 min. The resulting solution is cooled in an ice bath and treated with 1N hydrochloric acid (10 mL) to precipitate the product. Filtration and trituration of the damp cake with methanol (2 mL) gives pure product; mp 192-194°C (dec).

EXAMPLE 275.
3H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 2-benzoyl-4,5,6,7-tetrahydro-5-[(phenylamino)carbonyl]-3-(phenylmethyl)-; mp 140-145°C (dec).

EXAMPLE 276.
1H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 2-benzoyl-4,5,6,7-tetrahydro-5-[(phenylamino)carbonyl]-1-(phenylmethyl)-; mp 180-183°C (dec).

EXAMPLE 277.
3H-Imidazo[4,5-c]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-2-(4-methoxybenzoyl)-5-[(phenylamino)carbonyl]-3-phenylmethyl)-; mp 172-174°C (dec).

EXAMPLE 278.

(S)-1,4,6,7-tetrahydro-6-(t-butyldimethylsilyloxymethyl)-N-methyl-N-phenylmethyl)-5H-imidazo[4,5-c]pyridine-5-carboxamide.

A mixture of 2.7 g of (S)-4,5,6,7-tetrahydro-1-(phenylmethyl)-1H-imidazo[4,5-c]pyridine-6-carboxylic acid methyl ester and 50 mL of tetrahydrofuran is stirred at 0°C under a nitrogen atmosphere and 0.6 g at lithium aluminum hydride is slowly added. The ice bath is removed and the reaction mixture is allowed to stir for 15 hr. The mixture is quenched with 0.6 mL of water, 0.6 mL of a 15% sodium hydroxide solution and 1.7 mL of water and allowed to stir for 1 hr. The suspension is filtered and the filtrate is concentrated to give the amino alcohol as a light yellow solid, TLC (SiO_2) 10% MeOH/$CHCl_3$, R_f = 0.15.

A mixture of 0.7 g of the above amino alcohol, 0.96 g of t-butyldimethylsilyl chloride, 0.49 g of imidazole and 15 mL of dry dimethylformamide is stirred at room temperature for 18 hr. The reaction mixture is concentrated, diluted with ethyl acetate and washed twice with water and twice with saturated sodium bicarbonate. The organic layer is dried over magnesium sulfate, filtered and concentrated. The residue is purified by flash chromatography on silica gel eluting with a 2.5% methanol and chloroform mixture. The desired fractions are combined and collected to afford the silyl ether as an oil; TLC (SiO_2) 10% MeOH/$CHCl_3$, R_f = 0.55.

A mixture of 0.65 g of the above silyl ether 0.34 g of N-methyl, N-phenylcarbamoyl chloride, 0.56 mL of triethylamine and 10 mL dry tetrahydrofuran is stirred at room temperature for 24 hr. The reaction

mixture is filtered and concentrated. The residue is flash chromatographed on silica gel eluting with a 2% methanol and chloroform mixture. The desired fractions are combined and concentrated to afford (S)-1,4,6,7-tetrahydro-6-(t-butyldimethylsilyloxymethyl)-N-methyl-N-phenyl-1-phenylmethyl)-5H-imidazo[4,5-c]-pyridine-5-carboxamide as an oil; TLC (SiO_2) 10% $MeOH/CHCl_3$, R_f = 0.15.

EXAMPLE 279.

(S)-1,4,6,7-tetrahydro-6-(hydroxymethyl)-N-methyl-N-phenyl-1-(phenylmethyl)-5H-imidazo[4,5-c]pyridine-5-carboxamide.

A mixture of 3.80 g of (S)-1,4,6,7-tetrahydro-6-(t-butyldimethylsilyloxymethyl)-N-methyl-N-phenyl-1-(phenylmethyl)-5H-imidazo[4,5-c]pyridine-5-carboxamide and 100 mL of 2% hydrogen fluoride in acetonitrile (prepared by mixing 4 mL of a 48% aqueous hydrogen fluoride solution with 96 mL of acetonitrile) is stirred at room temperature for 1 hr. The solution is concentrated, diluted with ethyl acetate and washed with a saturated sodium bicarbonate solution. The organic layer is dried over magnesium sulfate, filtered and concentrated to dryness. The residue is purified by silica gel flash chromatography eluting with a 0-2% methanol in chloroform progression. The desired fractions are concentrated to afford (S-1,4,6,7-tetrahydro-6-(hydroxymethyl)-N-methyl-N-phenyl-1-(phenylmethyl)-5H-imidazo[4,5-c]pyridine-5-carboxamide as a white solid, mp 65-75°C.

EXAMPLE 280.

(S)-5-(diphenylacetyl)-1,4,6,7-tetrahydro-1-[(4-methoxy-3-methylphenyl)methyl]-1H-imidazo[4,5-c]-pyridine-6-methanol.

Following the procedure of Example 278 using (S)-4,5,6,7-tetrahydro-1-[(4-methoxy-3-methylphenyl)-methyl]-1H-imidazo[4,5-c]pyridine-6-carboxylic acid methyl ester as the starting material in the first step and acylating with diphenylacetyl chloride in the third step and desilylating following the procedure of Example 279 afforded the desired product, mp 164-170°C.

Using a process analogous to the above Examples 278 through 280 and using variations for the preparation of compounds of formula I above the following examples use appropriate corresponding starting materials for preparation of compound I as follows:

EXAMPLE 281.

1H-Imidazo[4,5-c]pyridine-6-methanol, 4,5,6,7-tetrahydro-5-(phenylacetyl)-1-(phenylmethyl)-, (S)-; mp 119-125°C.

EXAMPLE 282.

1H-Imidazo[4,5-c]pyridine-6-methanol, 4,5,6,7-tetrahydro-5-(2-phenylethyl)-1-(phenylmethyl)-; tlc (SiO_2) R_f 0.5 (1:4 MeOH/$CHCl_3$).

EXAMPLE 283.

1H-Imidazo[4,5-c]pyridine-6-methanol, 5-[bis(4-chlorophenyl)acetyl]-4,5,6,7-tetrahydro-1-[(3-methyl-4-nitro-phenyl)methyl]-, (S)-; mp 178-185°C.

EXAMPLE 284.
1H-Imidazo[4,5-c]pyridine-6-methanol, 5-(diphenylacetyl)-4,5,6,7-tetrahydro-1-[(3-methyl-4-nitrophenyl)methyl]-, (S)-; mp 187-195°C.

EXAMPLE 285.
1H-Imidazo[4,5-c]pyridine-6-methanol, 1-[[4-(dimethylamino)-3-methylphenyl]methyl]-5-(diphenylacetyl)-4,5,6,7-tetrahydro-, (S)-; mp 178-185°C.

EXAMPLE 286.
(S)-1,4,6,7-tetrahydro-2-bromo-6-(t-butyldimethylsilyloxymethyl)-N-methyl-N-phenyl-1-(phenylmethyl)-5H-imidazo[4,5-c]pyridine-5-carboxamide.

A mixture of 1.23 g of (S)-1,4,6,7-tetrahydro-6-(t-butyldimethylsilyloxymethyl)-N-methyl-N-phenyl-1-(phenylmethyl)-5H-imidazo[4,5-c]pyridine-5-carboxamide and 10 mL of methylene chloride is stirred at room temperature and 0.45 g of N-bromosuccinimide is added. The reaction mixture is stirred for 20 min and concentrated. The residue is purified by flash chromatography on silica gel eluting with a 50% ethyl acetate-hexane mixture. The desired fractions are combined and concentrated to afford the desired product as an oil; TLC (SiO_2) 50% EtOAc/hexane, R_f = 0.35.

EXAMPLE 287.
(S)-1,4,6,7-tetrahydro-2-butyl-6-(hydroxymethyl)-N-methyl-N-phenyl-1-(phenylmethyl)-5H-imidazo[4,5-c]-pyridine-5-carboxamide.

A mixture of 0.64 g of (S)-1,4,6,7-tetrahydro-2-bromo-6-(t-butyldimethylsilyloxymethyl)-N-methyl-N-phenyl-1-(phenylmethyl)-5H-imidazo[4,5-c]pyridine-5-carboxamide and 5 mL of tetrahydrofuran was cooled to -78°C under a nitrogen atmosphere and 0.48 mL of a 2.35 M solution of n-butyl lithium in hexane is added dropwise over a 5 min period. The solution is stirred for 15 min and a mixture of 0.14 g of n-butyl iodide in 1 mL of tetrahydrofuran is added dropwise over a 2 min period. After stirring at -78°C for 30 min the dry ice-acetone bath is removed and the reaction mixture is allowed to warm to room temperature overnight. The solution is concentrated, diluted with ethyl acetate and washed with saturated sodium bicarbonate. The organic layer is dried over magnesium sulfate, filtered and concentrated. The residue is purified by flash chromatography eluting with a 1-4% methanol in chloroform progression and the desired fractions are combined and concentrated to afford the product as an oil; TLC (SiO_2) 5% $MeOH/CHCl_3$, R_f = 0.5. Purification of the S isomer yielded a product having a mp of 70-75°C.

EXAMPLE 288.

(S)-1,4,6,7-tetrahydro-6-(t-butyldimethylsilyloxymethyl)-2-(hydroxyphenylmethyl)-1-(phenylmethyl-N-methyl-N-phenyl-5H-imidazo[4,5-c]pyridine-5-carboxamide.

Following the first step in the procedure outlined in Example 287 using the same starting material and benzeldehyde as the electrophile, the desired product can be prepared, TLC (S_iO_2) 10% $MeOH/CHCl_3$, R_f = 0.35.

EXAMPLE 289.

(S)-1,4,6,7-tetrahydro-6-(hydroxymethyl)-N-methyl-N-phenyl-1,2-bis(phenylmethyl)-5H-imidazo[4,5-c]-pyridine-5-carboxamide.

A mixture of 5.4 g of (S)-1,4,6,7-tetrahydro-6-(t-butyldimethylsilyloxymethyl)-2-(hydroxyphenyl-methyl)-1-(phenylmethyl)-N-methyl-N-phenyl-5H-imidazo-[4,5-c]pyridine-5-carboxamide, 1.1 g of acetic anhydride, 1.33 g of dimethylaminopyridine, 1.4 g of diisopropylethylamine and 50 mL of methylene chloride is stirred at room temperature for 15 hr. The solution is concentrated, diluted with ethyl acetate and washed with successive portions of water, saturated copper sulfate, water and saturated sodium bicarbonate. The organic layer is dried over magnesium sulfate, filtered and concentrated to afford the acetate as an oil; TLC (SiO_2) 10% MeOH/$CHCl_3$, R_f = 0.56.

The acetate (4.80 g) is desilylated using the procedure outlined in Example 279 to afford the alcohol, TLC (SiO_2) 10% MeOH/$CHCl_3$, R_f = 0.35, mp 80-87°C.

A mixture 1.5 g of the alcohol, 75 mL of methanol and 0.1 g of 20% palladium on charcoal catalyst is treated in a Parr pressure apparatus with hydrogen gas at an initial pressure of 50 psi at room temperature for 7 hr. The catalyst is removed by filtration and the filtrate is concentrated. The residue is purified by radial chromatography on a 4 mm silica gel plate eluting with a 0-3% methanol in chloroform progression. Concentration of the desired fractions affords the product as a white solid, mp 80-87°C.

EXAMPLE 290.

(S)-1,4,6,7-tetrahydro-6-(hydroxymethyl)-2-(hydroxyphenylmethyl)-1-(phenylmethyl)-N-methyl-N-phenyl-5H-imidazo[4,5-c]-pyridine-5-carboxamide.

Using (S)-1,4,6,7-tetrahydro-6-(t-butyldimethylsilyloxymethyl)-2-(hydroxyphenylmethyl)-1-(phenylmethyl)-N-methyl-N-phenyl-5H-imidazo[4,5-c]pyridine-5-carboxamide as the starting material and following the procedure outlined in Example 279 the product is obtained as a white solid, mp 107-120°C.

EXAMPLE 291.

5H-Imidazo[4,5-c]pyridine-5-carboxamide, 1,4,6,7-tetrahydro-6-(hydroxymethyl)-N,2-dimethyl-N-phenyl-1-(phenyl-methyl)-, (S)-; mp 130-135°C.

EXAMPLE 292.

5H-Imidazo[4,5-c]pyridine-5-carboxamide, 1,4,6,7-tetrahydro-2-[hydroxy-(4-methoxyphenyl)methyl]-6-hydroxymethyl)-N-methyl-N-phenyl-1-(phenylmethyl)-; mp 175-180°C.

EXAMPLE 293.

2-Bromo-8a,9-dihydro-7-phenyl-1-(phenylmethyl)-1H-diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione.

A solution of bromine (1.60 g) in methylene chloride is added slowly to a stirred mixture 3.6 g of the product from Example 152 in methylene chloride (150 mL). The resulting solution is stirred for 1/2 hr at room temperature, washed with water (150 mL), dried ($MgSO_4$) and concentrated to 20 mL. Addition of ethyl acetate (50 mL) resulted in precipitation of product. Recrystallization from dimethylformamide-ether gives pure compound, mp 267-269°C.

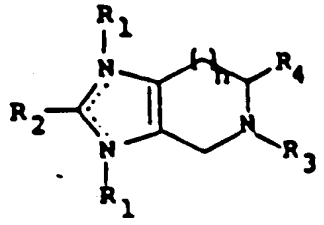
EXAMPLE 294.
1H-Imidazo[1,5-a:4',5'-d]pyridine-6-carboxylic acid, 2-bromo-4,5,6,7-tetrahydro-5-[(phenylamino)carbonyl]-1-(phenylmethyl)-; mp 270-275°C.

EXAMPLE 295.
3H-Diimidazo[1,5-a:4',5'-d]pyridine-6,8(4H,7H)-dione, 8a,9-dihydro-7-phenyl-2,3-bis(phenylmethyl)-; mp 181-182°C.

EXAMPLE 296.
3H-Imidazo[1,5-a:4',5'-d]pyridine-6-carboxylic acid, 4,5,6,7-tetrahydro-5-[(phenylamino)carbonyl]-2,3-bis-(phenylmethyl)-; mp 158-160°C (dec).

CLAIMS (for contracting states BE, CH, DE, FR, GB IT, LI, LU, NL, SE

1. A compound having the formula (I)



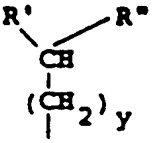
I

and their pharmaceutically acceptable base or acid addition salts; wherein

(1) - - - is a single or double bond;

(2) one of R_1 is present and is

(a) alkyl of from four to twenty carbons, inclusive,

(b)  wherein y is zero, one, two, three, four or five, R' is cycloalkyl, naphthyl, heteroaryl, phenyl unsubstituted or substituted with of from one through five, preferably one through three, substituents comprising lower alkyl, halo, trifluoromethyl, hydroxy, lower alkoxy, lower acyloxy, amino, N-lower monoalkylamino, N,N-lower dialkylamino, lower thioalkyl,

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lower alkylsulfonyl, nitro or $-NH\overset{O}{\overset{\|}{C}}R_{10}$ wherein R_{10} is lower alkyl, phenyl unsubstituted or substituted by lower alkyl, or $-NHR_{11}$ wherein R_{11} is hydrogen or lower alkyl, and R" is hydrogen, lower alkyl, cycloalkyl, naphthyl, phenyl unsubstituted or substituted with of from one through five substituents, preferably from one through three substituents, comprising alkyl, halo, trifluoromethyl, amino, N-lower monoalkylamino, N,N-lower dialkylamino, lower thioalkyl, lower alkylsulfonyl, or nitro;

(3) R_2 is

(a) hydrogen,

(b) halo,

(c) lower alkyl,

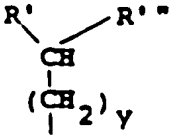
(d) $R'-(CH_2)_x$ wherein x is one, two, three, four, or five and R' is independently as defined above,

(e) $R'-\overset{O}{\overset{\|}{C}}-$ wherein R' is independently as defined above, or

(f) R'-CH(OH)- wherein R' is independently as defined above;

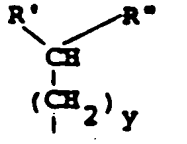
(4) R_3 is

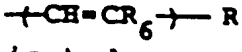
(a) $R'-(CH_2)_x$ wherein x and R' are independently as defined above,

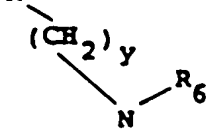
(b)  wherein R' and y are independently as defined above, and R'" is lower alkyl, cycloalkyl, naphthyl, phenyl unsubstituted or substituted with of from one through five substituents, preferably from one through three substituents, comprising alkyl, halo, trifluoromethyl, amino, N-lower monoalkylamino, N,N-lower dialkylamino, lower thioalkyl, lower alkylsulfonyl, or nitro;

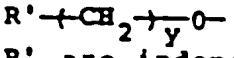
(c)  wherein R_5 is

(i) alkyl of from one to fifteen carbons, inclusive,

(ii)  wherein R', R" and y are independently as defined above,

(iv)  wherein R_6 is hydrogen or lower alkyl and R_1 is as defined above,

(v)  wherein y, R' and R_6 are independently as defined above,

(vi)  wherein y and R' are independently as defined above,

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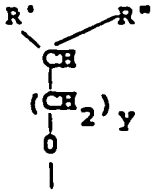
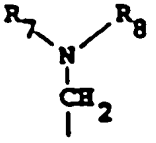
(vii)  wherein R', R", and y are independently as defined above,

(d) wherein R_5 is independently as defined above, preferably $R'-(CH_2)_y$ wherein R' and y are independently as defined above;

(5) R_4 is

(a) $-CH_2OR_7$ wherein R_7 is hydrogen, lower acyl, a lower alkyl,

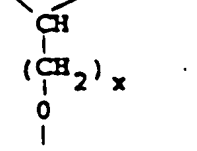
(b)  wherein R_7 is independently as defined above and R_8 is hydrogen, lower alkyl, or benzyl,

(c) ,

(d) $-C\equiv N$,

(e) wherein R_9 is hydrogen, lower alkyl or benzyl; and

(6) n is zero, one, two, or three; with the overall proviso that R_9 cannot be hydrogen

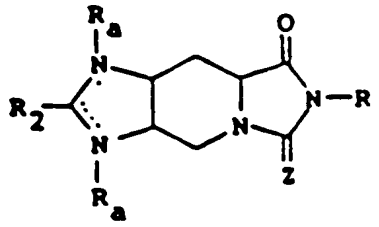
when R_3 is $R'-(CH_2)_x$ or  wherein R_5 is $R'-(CH_2)_y-O-$ or  wherein

each of R', R", x and y are as defined above.

2. A compound of claim 1 wherein R_2 is H, n is one or two, and R_3 is $-\overset{O}{\overset{\|}{C}}R_5$ or $-\overset{O}{\overset{\|}{\underset{O}{\overset{\|}{S}}}}R_5$ wherein R_5 is as defined above and R_4 is as defined above.

3. A compound of claim 2 wherein R_3 is $-\overset{O}{\overset{\|}{C}}R_5$ wherein R_5 is as defined above.

4. A compound having the formula (II)



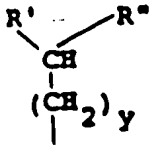
II

and the nontoxic, pharmaceutically acceptable base or acid addition salts thereof, wherein - - - is a single or double bond;

(1) one of R_a is present and is

(a) hydrogen,

(b) alkyl of from one to twenty carbons, inclusive,

(c)  wherein y is zero, one, two, three, four or five and R' is cycloalkyl, naphthyl, heteroaryl, phenyl unsubstituted or substituted with of from one through five, preferably one through three, substituents comprising lower alkyl, halo, trifluoromethyl, hydroxy, lower alkoxy, lower acyloxy, amino, N-lower monoalkylamino, N,N-lower dialkylamino, lower thioalkyl, lower alkylsulfonyl, nitro or $-NHCR_{10}$ wherein R_{10} is lower alkyl, phenyl unsubstituted or substituted by lower alkyl, or $-NHR_{11}$ wherein R_{11} is hydrogen or lower alkyl, and R" is hydrogen, lower alkyl, cycloalkyl, naphthyl, phenyl unsubstituted or substituted with of from one through five substituents, preferably from one through three substituents, comprising alkyl, halo, trifluoromethyl, anino, N-lower monoalkylamino, N,N-lower dialkylamino, lower thioalkyl, lower alkylsulfonyl, or nitro;

(2) Z is oxygen or sulfur; and

(3) R_2 is

(a) hydrogen,

(b) halo,

(c) lower alkyl,

(d) $R'-(CH_2)_x$ wherein x is one, two, three, four, or five and R' is independently as defined above,

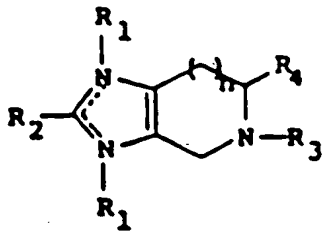
(e) $R'-\overset{O}{\overset{\|}{C}}-$ wherein R' is independently as defined above, or

(f) R'-CH(OH)- wherein R' is independently as defined above;

(4) R is selected from the group consisting of lower alkyl, heteroaryl, and phenyl or benzyl each unsubstituted or substituted with of from one through five substituents comprising lower alkyl, halo, trifluoromethyl, hydroxy, lower alkoxy, lower acyloxy, amino, N-lower monoamino, N,N-lower dialkylamino, lower thioalkyl, lower alkylsulfonyl, or nitro.

5. A compound according to claim 4 wherein Z is as defined above and R is branched alkyl of from three to five carbons, inclusive, or phenyl substituted by one, two or three methoxy groups.

6. A pharmaceutical composition for treating hypertension in mammals comprising an antihypertensive effective amount of the compound of formula (I')



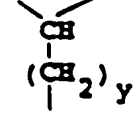
I'

and their pharmaceutically acceptable base or acid addition salts; wherein

(1) - - - is a single or double bond;

(2) one of R_1 is present and is

(a) alkyl of from four to twenty carbons, inclusive,

(b)  wherein y is zero, one, two, three, four or five, R' is cycloalkyl, naphthyl, heteroaryl, phenyl unsubstituted or substituted with of from one through five, preferably one through three, substituents comprising lower alkyl, halo, trifluoromethyl, hydroxy, lower alkoxy, lower acyloxy, amino, N-lower monoalkylamino, N,N-lower dialkylamino, lower thioalkyl, lower alkylsulfonyl, nitro or $-NHCR_{10}$ wherein R_{10} is lower alkyl, phenyl unsubstituted or substituted by lower

alkyl, or $-NHR_{11}$ wherein R_{11} is hydrogen or lower alkyl, and R" is hydrogen, lower alkyl, cycloalky, naphthyl, phenyl unsubstituted or substituted with of from one through five substituents, preferably from one through three substituents, comprising alkyl, halo, trifluoromethyl, amino, N-lower monoalkylamino, N,N-lower dialkylamino, lower thioalkyl, lower alkylsulfonyl, or nitro;

(3) R_2 is

(a) hydrogen,

(b) halo,

(c) lower alkyl,

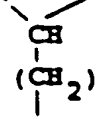
(d) $R'-(-CH_2-)_x$ wherein x is one, two, three, four, or five and R' is independently as defined above,

(e) $R'-\overset{O}{\overset{\|}{C}}-$ wherein R' is independently as defined above, or

(f) R'-CH(OH)- wherein R' is independently as defined above;

(4) R_3 is

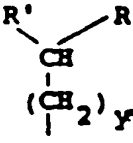
(a) $R'-(-CH_2-)_x$ wherein x and R' are independently as defined above,

(b)  wherein R' and y are independently as defined above, and R'" is lower alkyl, cycloalkyl, naphthyl, phenyl unsubstituted or substituted with of from one through five substituents,

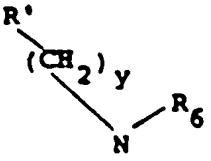
preferably from one through three substituents, comprising alkyl, halo, trifluoromethyl, amino, N-lower monoalkylamino, N,N-lower dialkylamino, lower thioalkyl, lower alkylsulfonyl, or nitro;

(c) $-\overset{O}{\overset{\|}{C}}-R_5$ wherein R_5 is

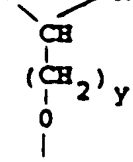
(i) alkyl of from one to fifteen carbons, inclusive,

(ii)  wherein R', R" and y are independently as defined above,

(iv) $-(CH=CR_6)-R_1$, wherein R_6 is hydrogen or lower alkyl and R_1 is as defined above,

(v)  wherein y, R' and R_6 are independently as defined above,

(vi) $R'-(CH_2)_y-O-$ wherein y and R' are independently as defined above,

(vii)  wherein R', R", and y are independently as defined above,

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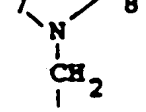
(d) $-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-R_5$ wherein R_5 is independently as defined above, preferably $R'-(CH_2)_y$ wherein R' and y are independently as defined above;

(5) R_4 is

(a) $-CH_2OR_7$ wherein R_7 is hydrogen, lower acyl, a lower alkyl,

(b)  wherein R_7 is independently as defined above and R_8 is hydrogen, lower alkyl, or benzyl,

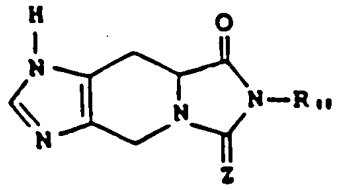
(c) $-\overset{\overset{O}{\|}}{C}H$,

(d) $-C\equiv N$,

(e) $-\overset{\overset{O}{\|}}{C}OR_9'$ wherein R_9' is hydrogen, lower alkyl or benzyl; and

(6) n is zero, one, two, or three; together with a pharmaceutically acceptable carrier.

7. A pharmaceutical composition for treating hypertension in mammals comprising an antihypertensive effective amount of the compound of formula (IIa)



IIa

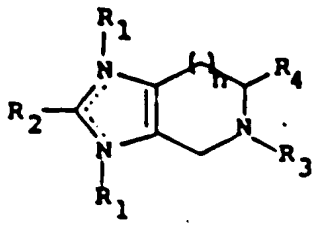
wherein Z is oxygen or sulfur and R_{11} is branched alkyl of from three to five carbons, inclusive, and substituted phenyl, and a pharmaceutically acceptable carrier.

8. A composition of claim 7 wherein R_{11} is branched alkyl of from three to five carbons, inclusive and phenyl substituted by one to three methoxy groups.

9.) Use of a compound of formula I' according to claim 6 for the manufacture of a medicament for treating hypertension in mammals suffering therefrom.

10.) Use of a compound of formula IIa according to claim 7 for the manufacture of a medicament for treating hypertension in mammals suffering therefrom.

11.) A process for preparing a compound having the formula (I)

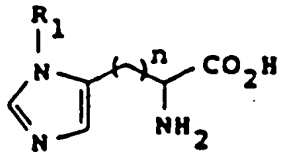


in accordance with claims 1 to 3,
wherein R_1, R_2, R_3, R_4 and n have the above mentioned meaning,
and their pharmaceutically acceptable base or acid addition salts,

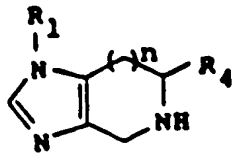
comprising

(A) contacting

a compound of the formula



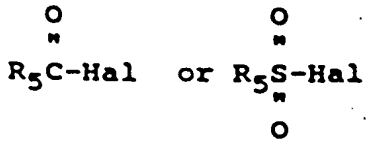
wherein R_1 and n are as defined above, with formaldehyde or a formaldehyde equivalent such as dimethoxymethane in the presence of a strong acid such as hydrochloric acid to give a compound of the formula III



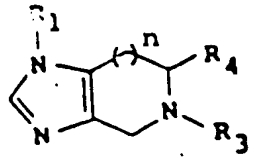
III

wherein R_1 n and R_4 are as defined above,

(B) and further a compound of the formula III is contacted with an activated acylating derivative of R_5CO_2H or R_5 SO_3H or a compound of formula III wherein R_4 is $-CO_2H$, is acylated in aqueous basic solution with selected compounds of the formula



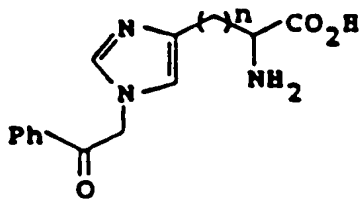
wherein Hal is halo and R_5 is as defined above to give a compound of formula I



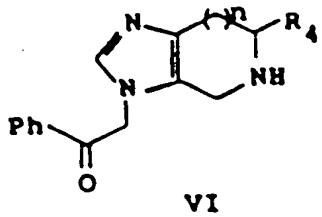
wherein R_1, R_4 and n are as defined above and R_3 is

wherein R_5 is as defined above or

(C) contacting
a compound of the formula



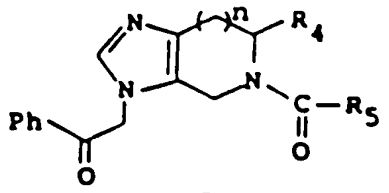
wherein n is as defined above with acidic formaldehyde to give a compound of the formula VI



VI

wherein R_4 and n are as defined above and Ph is a phenyl radical.

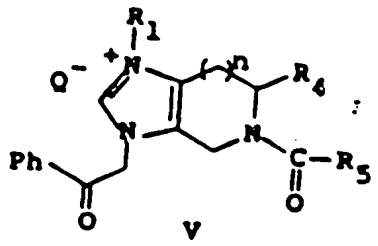
(D) and further the compound of the formula VI is contacted with an activated acylating derivative such as described above to give a compound of the formula IV



IV

wherein R_4, R_5 and n are as defined above,

(E) a) and further the compound of the formula IV is contacted with R_1-Q wherein Q may be halo or sulfonate and trifluorosulfonate ester of R_1-OH wherein R_1 is as defined above to give the intermediate salt of formula V



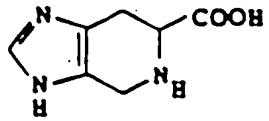
V

wherein R_1, R_4, R_5 and n are as defined above,

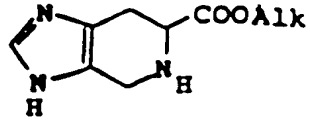
(b) and further deprotecting and optionally reacting the product of step (c) to obtain the compound of formula I wherein R_3 is as defined above.

(F) contacting

(a) a compound of the formula

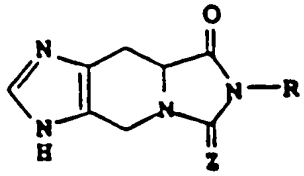


or



with an RN=C=O or RN=C=S, wherein R is selected from the group consisting of lower alkyl, heteroaryl, and phenyl or benzyl each unsubstituted or substituted with of from one through five substituents comprising lower alkyl, halo, trifluoromethyl, hydroxy, lower alkoxy, lower acyloxy,

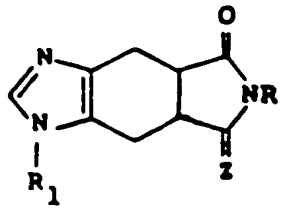
amino, N-lower monoamino, N,N-lower dialkylamino, lower thioalkyl, lower alkylsulfonyl, or nitro and Alk is a lower alkyl group to give a compound of the formula VII



VII

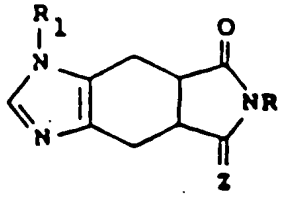
wherein Z is oxygen or sulfur and R is as defined above,

(b) and further the compound of formula VII is contacted with R_1-Q as defined above in the presence of a strong base such as sodium or potassium hydride or sodium alkylate to give a mixture having the compound of formula VIII



VIII

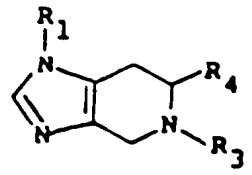
wherein Z, R and R_1 are as defined above and a compound of formula IX



IX

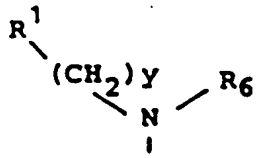
wherein Z, R and R_1 are as defined above which is optionally separated by crystallisation or chromatography.

(c) and further the compounds of formula VIII or IX and hydrolyzed under moderate basic conditions such as alkali hydride to give a compound of formula I



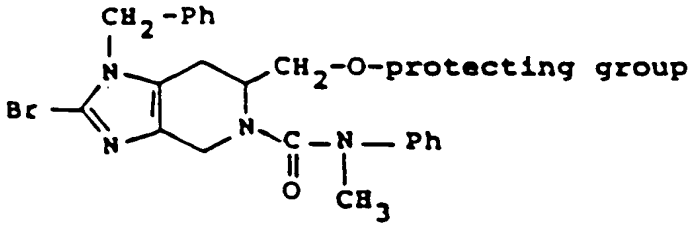
I

wherein R_5 is



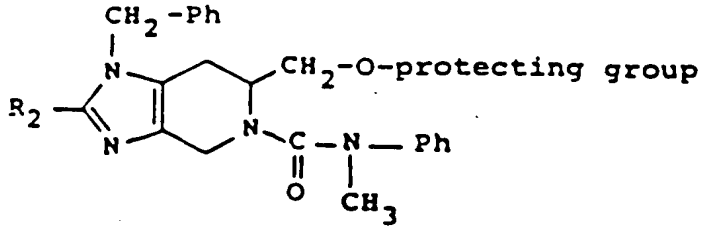
wherein R_1 and Y are as defined above and R_6 is H, or under more rigorous basic conditions such as concentrated alkali hydroxide to give intermediate of formula III wherein R_4 is CO_2H.

(G) Additionally
a compound of the formula I wherein R_2 is H, R_4 is as defined above, R_4 is CH_2O-R_1 and R_3 is COR_5 wherein R_4, R_3 and R_5 are as defined above, a compound of the formula VIII or IX as defined above is contacted with a brominating agent such as bromine or N-bromo-succinimide to give an intermediate of the formula



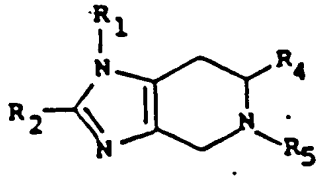
or

(H) (a) and further this intermediate is contacted with an alkyllithium reagent such as n-butyllithium to form a lithio-derivative which is further contacted with an alkylating agent R_2-Q, where R_2 and Q are as described above, an aldehyde or ketone or an appropriate carboxylic acid derivative to give an intermediate of the formula



wherein R_2 and Ph is as described above,

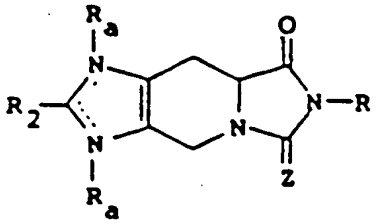
(b) and further processing of the intermediate as described above gives a compound of formula I



I

wherein R_1, R_2, R_4, and R_5 have the above mentioned meaning.

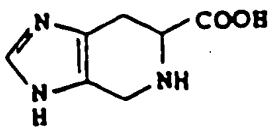
12.) A process for preparing a compound having the formula II



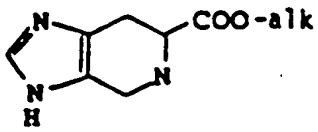
according to claims 4 and 5,
wherein R_a, R_2, Z and R have the above mentioned meaning
and the nontoxic, pharmaceutically acceptable base
or acid addition salts thereof,

comprising

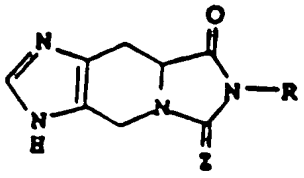
(A) contacting
a compound of the formula



or



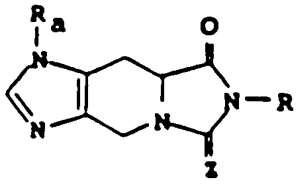
wherein alk is a lower alkyl group with an RN=C=O or RN=C=S, wherein R is as defined above to give a compound of the formula VII



VII

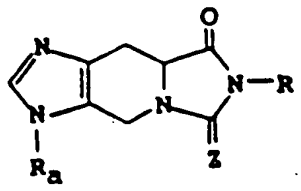
wherein Z and R are as defined above

(B) and further compound of formula VII is contacted with R_a-Q as defined above in the presence of a strong base such as sodium or potassium hydride or sodium alkylate to give a mixture of a compound of formula VIII



VIII

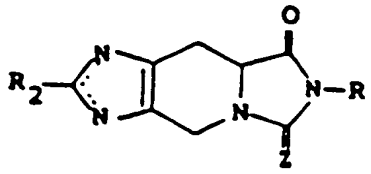
wherein Z, R and R_a are as defined above and a compound of formula IX



IX

wherein Z, R and R_a are as defined above, which is optionally separated by crystallization or chromatography; or

(C) and further compounds of formula VIII or IX both as defined above when Z is O, may be contacted with an aroylhalide in the presence of a tertiary organic base such as triethylamine to give compounds of formula II

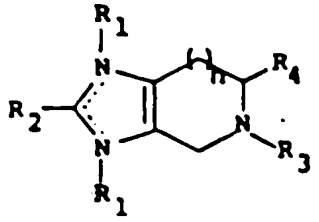


II

where R_2 is $R'C(=O)-$, wherein R' is as defined above and where this group may further be reduced and deoxygenated using methods known in the art to produce other R_2 substituents as defined above.

CLAIMS (for contracting states AT, ES, GR

1.) A process for preparing a compound having the formula (I)



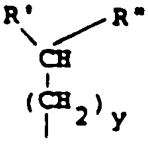
I

and their pharmaceutically acceptable base or acid addition salts; wherein

(1) - - - is a single or double bond;

(2) one of R_1 is present and is

(a) alkyl of from four to twenty carbons, inclusive,

(b)  wherein y is zero, one, two, three, four or five, R' is cycloalkyl, naphthyl, heteroaryl, phenyl unsubstituted or substituted with of from one through five, preferably one through three substituents, comprising lower alkyl, halo, trifluoromethyl, hydroxy, lower alkoxy, lower acyloxy, amino, N-lower monoalkylamino, N,N-lower dialkylamino, lower thioalkyl,

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lower alkylsulfonyl, nitro or $-NH\overset{O}{\overset{\|}{C}}R_{10}$ wherein R_{10} is lower alkyl, phenyl unsubstituted or substituted by lower alkyl, or $-NHR_{11}$ wherein R_{11} is hydrogen or lower alkyl, and R" is hydrogen, lower alkyl, cycloalkyl, naphthyl, phenyl unsubstituted or substituted with of from one through five substituents, preferably from one through three substituents, comprising alkyl, halo, trifluoromethyl, amino, N-lower monoalkylamino, N,N-lower dialkylamino, lower thioalkyl, lower alkylsulfonyl, or nitro;

(3) R_2 is

(a) hydrogen,

(b) halo,

(c) lower alkyl,

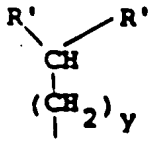
(d) $R'-(CH_2)_x$ wherein x is one, two, three, four, or five and R' is independently as defined above,

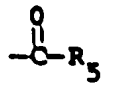
(e) $R'-\overset{O}{\overset{\|}{C}}-$ wherein R' is independently as defined above, or

(f) R'-CH(OH)- wherein R' is independently as defined above;

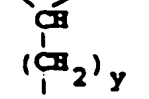
(4) R_3 is

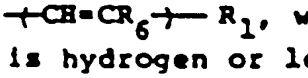
(a) $R'-(CH_2)_x$ wherein x and R' are independently as defined above,

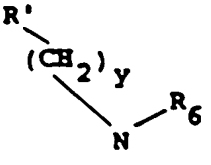
(b)  wherein R' and y are independently as defined above, and R'" is lower alkyl, cycloalkyl, naphthyl, phenyl unsubstituted or substituted with of from one through five substituents, preferably from one through three substituents, comprising alkyl, halo, trifluoromethyl, amino, N-lower monoalkylamino, N,N-lower dialkylamino, lower thioalkyl, lower alkylsulfonyl, or nitro;

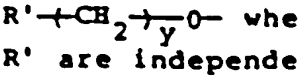
(c)  wherein R_5 is

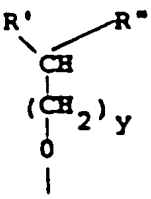
(i) alkyl of from one to fifteen carbons, inclusive,

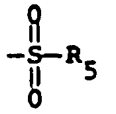
(ii)  wherein R', R" and y are independently as defined above,

(iv)  wherein R_6 is hydrogen or lower alkyl and R_1 is as defined above,

(v)  wherein y, R' and R_6 are independently as defined above,

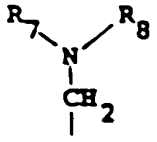
(vi)  wherein y and R' are independently as defined above,

(vii)  wherein R', R", and y are independently as defined above,

(d)  wherein R_5 is independently as defined above, preferably $R'\text{-}(CH_2)_y$ wherein R' and y are independently as defined above;

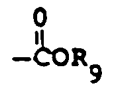
(5) R_4 is

(a) $-CH_2OR_7$ wherein R_7 is hydrogen, lower acyl, a lower alkyl,

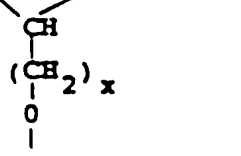
(b)  wherein R_7 is independently as defined above and R_8 is hydrogen, lower alkyl, or benzyl,

(c)  ,

(d) $-C{\equiv}N$,

(e)  wherein R_9 is hydrogen, lower alkyl or benzyl; and

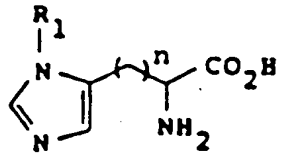
(6) n is zero, one, two, or three; with the overall proviso that R_9 cannot be hydrogen

when R_3 is $R'\text{-}(CH_2)_x$ or  wherein R_5 is $R'\text{-}(CH_2)_y\text{-}O\text{-}$ or  wherein

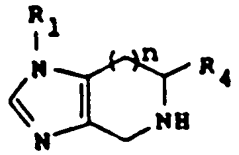
each of R', R", x and y are as defined above; and which comprises

(A) contacting

a compound of the formula



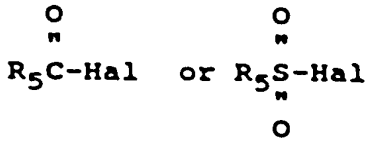
wherein R_1 and n are as defined above, with formaldehyde or a formaldehyde equivalent such as dimethoxymethane in the presence of a strong acid such as hydrochloric acid to give a compound of the formula III



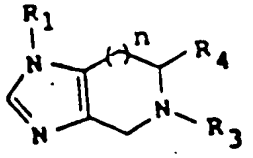
III

wherein R_1 n and R_4 are as defined above,

(B) and further a compound of the formula III is contacted with an activated acylating derivative of R_5CO_2H or R_5SO_3H or a compound of formula III wherein R_4 is $-CO_2H$, is acylated in aqueous basic solution with selected compounds of the formula



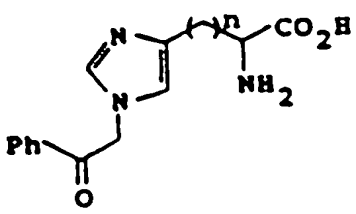
wherein Hal is halo and R_5 is as defined above to give a compound of formula I



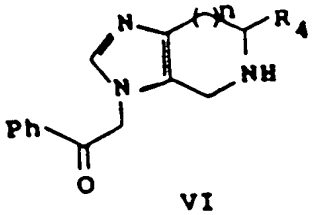
wherein R_1, R_4 and n are as defined above and R_3 is

wherein R_5 is as defined above or

(C) contacting
a compound of the formula



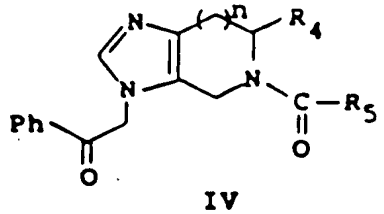
wherein n is as defined above with acidic formaldehyde to give a compound of the formula VI



VI

wherein R_4 and n are as defined above and Ph is a phenyl radical.

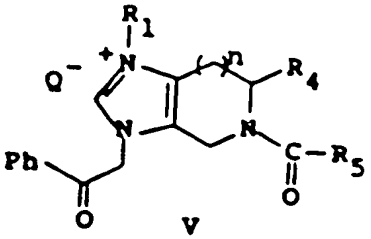
(D) and further the compound of the formula VI is contacted with an activated acylating derivative such as described above to give a compound of the formula IV



IV

wherein R_4, R_5 and n are as defined above,

(E) a) and further the compound of the formula IV is contacted with R_1-Q wherein Q may be halo or sulfonate and trifluorosulfonate ester of R_1-OH wherein R_1 is as defined above to give the intermediate salt of formula V



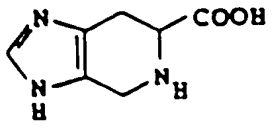
V

wherein R_1, R_4, R_5 and n are as defined above,

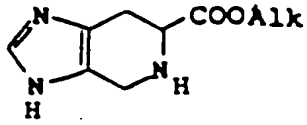
(b) and further deprotecting and optionally reacting the product of step (c) to obtain the compound of formula I wherein R_3 is as defined above.

(F) contacting

(a) a compound of the formula

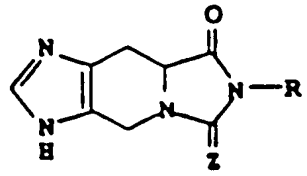


or



with an RN=C=O or RN=C=S, wherein R is selected from the group consisting of lower alkyl, heteroaryl, and phenyl or benzyl each unsubstituted or substituted with of from one through five substituents comprising lower alkyl, halo, trifluoromethyl, hydroxy, lower alkoxy, lower acyloxy,

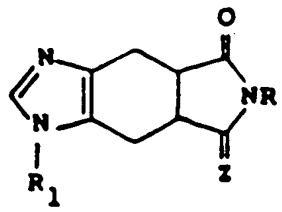
amino, N-lower monoamino, N,N-lower dialkylamino, lower thioalkyl, lower alkylsulfonyl, or nitro and Alk is a lower alkyl group to give a compound of the formula VII



VII

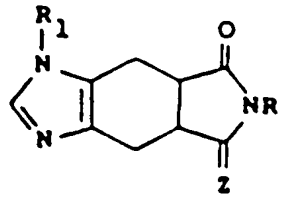
wherein Z is oxygen or sulfur and R is as defined above,

(b) and further the compound of formula VII is contacted with R_1-Q as defined above in the presence of a strong base such as sodium or potassium hydride or sodium alkylate to give a mixture having the compound of formula VIII



VIII

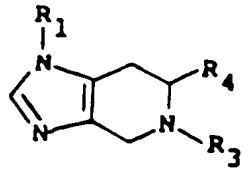
wherein Z, R and R_1 are as defined above and a compound of formula IX



IX

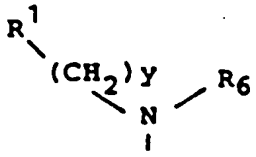
wherein Z, R and R_1 are as defined above which is optionally separated by crystallisation or chromatography.

(c) and further the compounds of formula VIII or IX and hydrolyzed under moderate basic conditions such as alkali hydride to give a compound of formula I



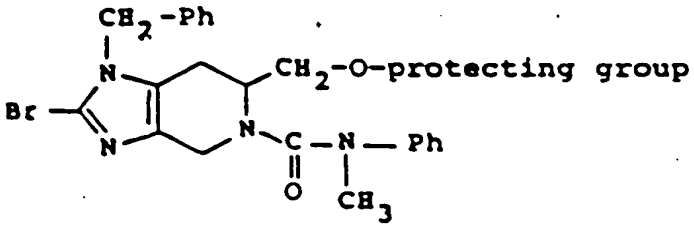
I

wherein R_5 is



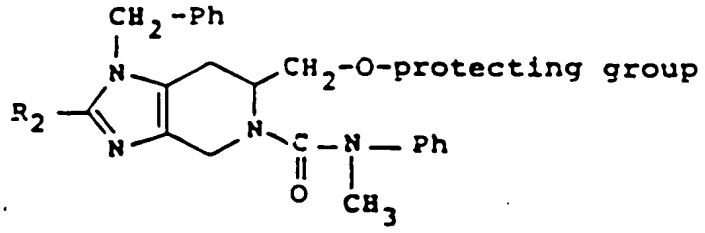
wherein R_1 and Y are as defined above and R_6 is H, or under more rigorous basic conditions such as concentrated alkali hydroxide to give intermediate of formula III wherein R_4 is CO_2H.

(G) Additionally
a compound of the formula I wherein R_2 is H, R_4 is as defined above, R_4 is CH_2O-R_1 and R_3 is COR_5 wherein R_4, R_3 and R_5 are as defined above, a compound of the formula VIII or IX as defined above is contacted with a brominating agent such as bromine or N-bromo-succinimide to give an intermediate of the formula



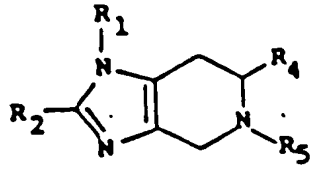
or

(H) (a) and further this intermediate is contacted with an alkyllithium reagent such as n-butyllithium to form a lithio-derivative which is further contacted with an alkylating agent R_2-Q, where R_2 and Q are as described above, an aldehyde or ketone or an appropriate carboxylic acid derivative to give an intermediate of the formula



wherein R_2 and Ph is as described above,

(b) and further processing of the intermediate as described above gives a compound of formula I



I

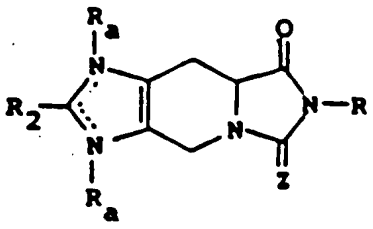
wherein R_1, R_2, R_4, and R_5 have the above mentioned meaning

2.) A process according to claim 1 wherein R_2 is H, n is one or two, and R_3 is $-\overset{\overset{O}{\|}}{C}R_5$ or $-\overset{\overset{O}{\|}}{S}R_5$ wherein R_5 is as defined above and R_4 is as defined above.

3.) A process according to claim 2

wherein R_3 is $-\overset{O}{\overset{\|}{C}}R_5$ wherein R_5 is as defined above.

4.) A process for preparing a compound having the formula II



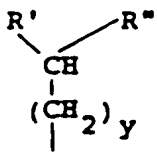
II

and the nontoxic, pharmaceutically acceptable base or acid addition salts thereof, wherein - - - is a single or double bond;

(1) one of R_a is present and is

(a) hydrogen,

(b) alkyl of from one to twenty carbons, inclusive,

(c)  wherein y is zero, one, two, three, four or five and R' is cycloalkyl, naphthyl, heteroaryl, phenyl unsubstituted or substituted with of from one through five, preferably one through three, substituents comprising lower alkyl, halo, trifluoromethyl, hydroxy, lower alkoxy, lower acyloxy, amino, N-lower monoalkylamino, N,N-lower dialkylamino, lower thioalkyl, lower alkylsulfonyl, nitro or $-NHCR_{10}$ wherein R_{10} is lower alkyl, phenyl unsubstituted or substituted by lower alkyl, or $-NHR_{11}$ wherein R_{11} is hydrogen or lower alkyl, and R" is hydrogen, lower alkyl, cycloalkyl, naphthyl, phenyl unsubstituted or substituted with of from one through five substituents, preferably from one through three substituents, comprising alkyl, halo, trifluoromethyl, anino, N-lower monoalkylamino, N,N-lower dialkylamino, lower thioalkyl, lower alkylsulfonyl, or nitro;

(2) Z is oxygen or sulfur; and

(3) R_2 is

(a) hydrogen,

(b) halo,

(c) lower alkyl,

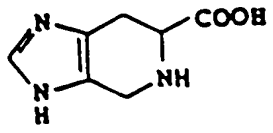
(d) $R'-(CH_2)_x$ wherein x is one, two, three, four, or five and R' is independently as defined above,

(e) $R'-\overset{O}{\overset{\|}{C}}-$ wherein R' is independently as defined above, or

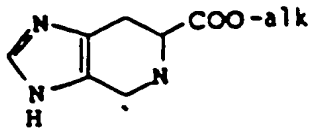
(f) R'—CH(OH)— wherein R' is independently as defined above;

(4) R is selected from the group consisting of lower alkyl, heteroaryl, and phenyl or benzyl each unsubstituted or substituted with of from one through five substituents comprising lower alkyl, halo, trifluoromethyl, hydroxy, lower alkoxy, lower acyloxy, amino, N-lower monoamino, N,N-lower dialkylamino, lower thioalkyl, lower alkylsulfonyl, or nitro; and which comprises

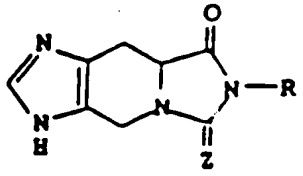
(A) contacting a compound of the formula



or



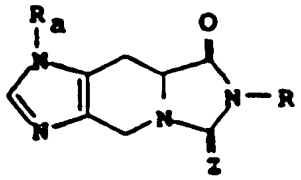
wherein alk is a lower alkyl group with an RN=C=O or RN=C=S, wherein R is as defined above to give a compound of the formula VII



VII

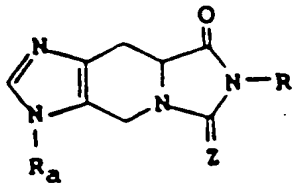
wherein Z and R are as defined above

(B) and further compound of formula VII is contacted with R_a-Q as defined above in the presence of a strong base such as sodium or potassium hydride or sodium alkylate to give a mixture of a compound of formula VIII



VIII

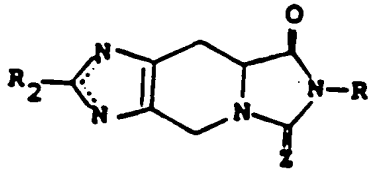
wherein Z, R and R_a are as defined above and a compound of formula IX



IX

wherein Z, R and R_a are as defined above, which is optionally separated by crystallization or chromatography; or

(C) and further compounds of formula VIII or IX both as defined above when Z is O, may be contacted with an aroylhalide in the presence of a tertiary organic base such as triethylamine to give compounds of formula II

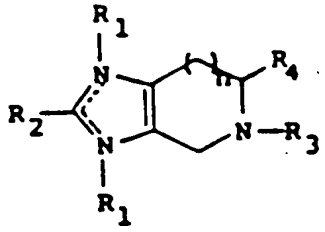


II

where R_2 is $R'C(=O)-$, wherein R' is as defined above and where this group may further be reduced and deoxygenated using methods known in the art to produce other R_2 substituents as defined above.

5.) A process according to claim 4 wherein Z is as defined above and R is branched alkyl of from three to five carbons, inclusive, or phenyl substituted by one, two or three methoxy groups.

6.) Use of a compound of formula (I')



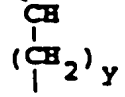
I'

and their pharmaceutically acceptable base or acid addition salts; wherein

(1) - - - is a single or double bond;

(2) one of R_1 is present and is

(a) alkyl of from four to twenty carbons, inclusive,

(b)  wherein y is zero, one, two, three, four or five, R' is cycloalkyl, naphthyl, heteroaryl, phenyl unsubstituted or substituted with of from one through five, preferably one through three, substituents comprising lower alkyl, halo, trifluoromethyl, hydroxy, lower alkoxy, lower acyloxy, amino, N-lower monoalkylamino, N,N-lower dialkylamino, lower thioalkyl, lower alkylsulfonyl, nitro or $-NHCR_{10}$ (with O) wherein R_{10} is lower alkyl, phenyl unsubstituted or substituted by lower

alkyl, or $-NHR_{11}$ wherein R_{11} is hydrogen or lower alkyl, and R" is hydrogen, lower alkyl, cycloalky, naphthyl, phenyl unsubstituted or substituted with of from one through five substituents, preferably from one through three substituents, comprising alkyl, halo, trifluoromethyl, amino, N-lower monoalkylamino, N,N-lower dialkylamino, lower thioalkyl, lower alkylsulfonyl, or nitro;

(3) R_2 is

(a) hydrogen,

(b) halo,

(c) lower alkyl,

(d) $R'-(CH_2)_x$ wherein x is one, two, three, four, or five and R' is independently as defined above,

(e) $R'-\overset{O}{\overset{\|}{C}}-$ wherein R' is independently as defined above, or

(f) R'-CH(OH)- wherein R' is independently as defined above;

(4) R_3 is

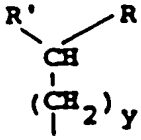
(a) $R'-(CH_2)_x$ wherein x and R' are independently as defined above,

(b) wherein R' and y are independently as defined above, and R'" is lower alkyl, cycloalkyl, naphthyl, phenyl unsubstituted or substituted with of from one through five substituents,

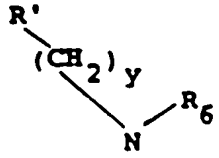
preferably from one through three substituents, comprising alkyl, halo, trifluoromethyl, amino, N-lower monoalkylamino, N,N-lower dialkylamino, lower thioalkyl, lower alkylsulfonyl, or nitro;

(c) $-\overset{O}{\overset{\|}{C}}-R_5$ wherein R_5 is

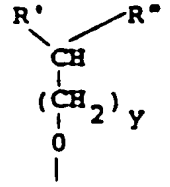
(i) alkyl of from one to fifteen carbons, inclusive,

(ii)  wherein R', R" and y are independently as defined above,

(iv) $-(CH=CR_6)-R_1$, wherein R_6 is hydrogen or lower alkyl and R_1 is as defined above,

(v)  wherein y, R' and R_6 are independently as defined above,

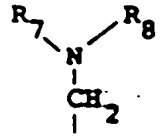
(vi) $R'-(CH_2)_y-O-$ wherein y and R' are independently as defined above,

(vii)  wherein R', R", and y are independently as defined above,

(d) $-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-R_5$ wherein R_5 is independently as defined above, preferably $R'-(-CH_2-)_y$ wherein R' and y are independently as defined above;

(5) R_4 is

(a) $-CH_2OR_7$ wherein R_7 is hydrogen, lower acyl, a lower alkyl,

(b)  wherein R_7 is independently as defined above and R_8 is hydrogen, lower alkyl, or benzyl,

(c) $-\overset{\overset{O}{\|}}{C}H$,

(d) $-C\equiv N$,

(e) $-\overset{\overset{O}{\|}}{C}OR_9'$ wherein R_9' is hydrogen, lower alkyl or benzyl; and

(6) n is zero, one, two, or three; together with a pharmaceutically acceptable carrier for the manufacture of a medicament for treating hypertension in mammals.

European Patent Office

EUROPEAN SEARCH REPORT

0245637

Application number

EP 87104736.1

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
D,A	PATENT ABSTRACTS OF JAPAN, unexamined applications, field C, vol. 8, no. 205, September 19, 1984 THE PATENT OFFICE JAPANESE GOVERNMENT page 125 C 243 • Kokai-no. 59-95 286 (OTSUKA) •	1,6,9	C 07 D 471/04 C 07 D 471/14 C 07 D 487/04 A 61 K 31/435
D,A	DE - A1 - 3 521 303 (FARMITALIA) • Abstract; page 15, line 21 - page 16, line 2 • & BE-A-902 611	1,6,9, 11	
D,A	US - A - 4 141 899 (ARCARI) • Abstract •	1,6,9	
A	US - A - 4 223 146 (ARCARI) • Abstract •	1,6,9	TECHNICAL FIELDS SEARCHED (Int. Cl. 4) C 07 D 471/00 C 07 D 487/00
A	US - A - 3 958 976 (GODDARD) • Columns 3,4, steps 2,3 •	4,12	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	23-06-1987	ONDER

CATEGORY OF CITED DOCUMENTS

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T : theory or principle underlying the invention
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